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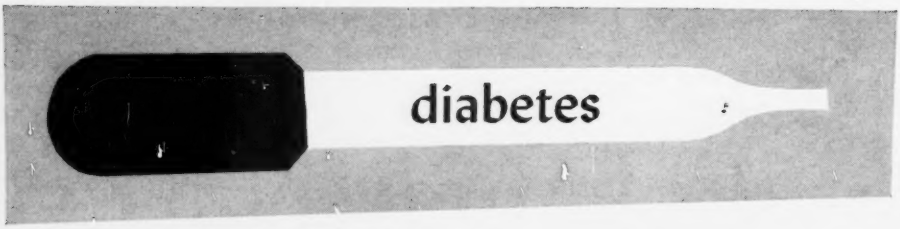

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2. Steine, L.: GP *8*:45 (July) 1953.

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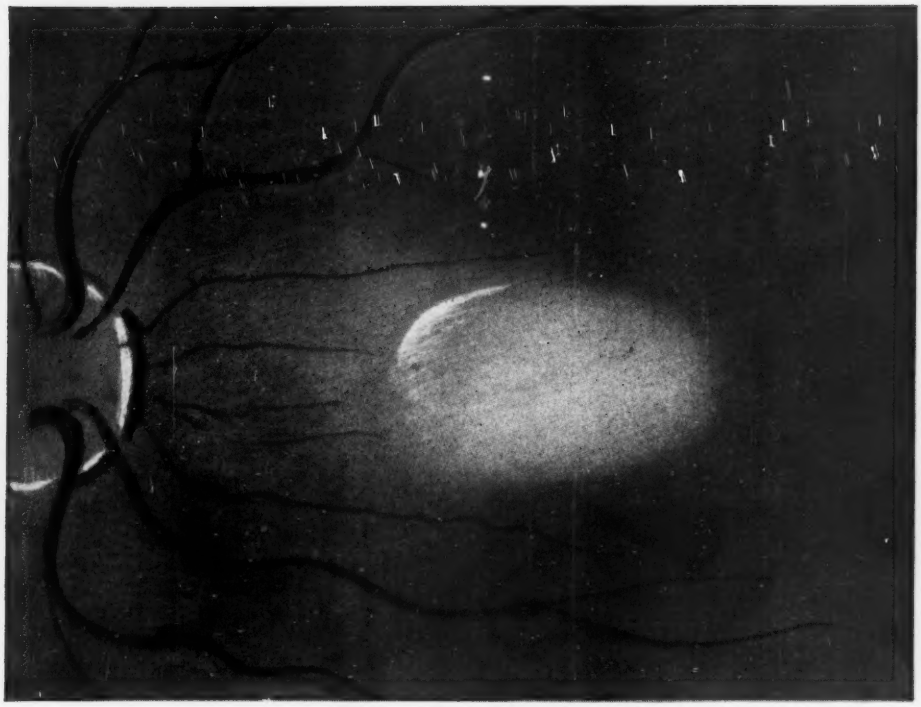

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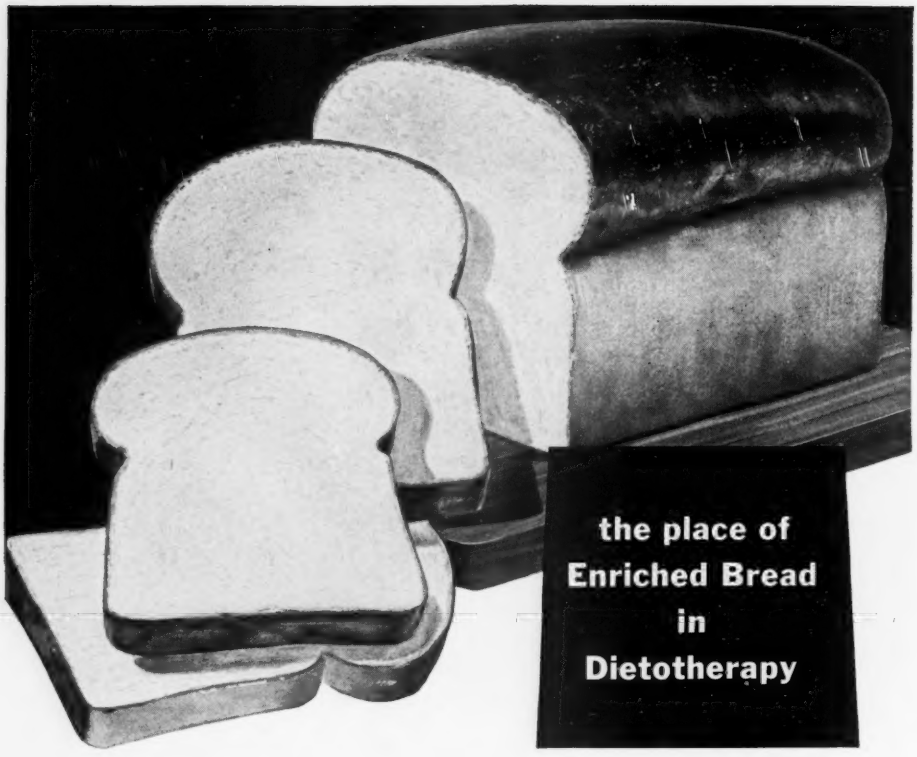

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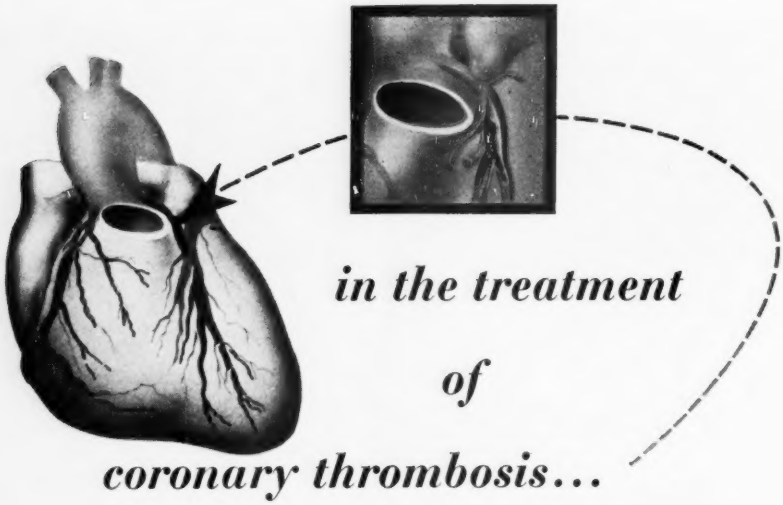

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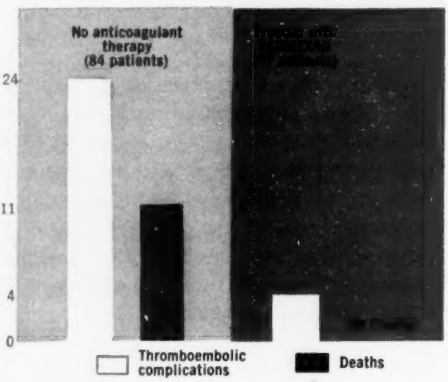

1. Tulloch, J. A., and Gilchrist, A. R.: Tromexan in the Treatment of Coronary Thrombosis, Am. Heart J. 42:864, 1951.

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PORPHYRIN CONTENT OF BONE MARROW AND LIVER IN THE VARIOUS FORMS OF PORPHYRIA

RUDI SCHMID, M.D.
SAMUEL SCHWARTZ, M.D.
AND
C. J. WATSON, M.D.
MINNEAPOLIS

THE CLASSIFICATION of porphyria in the past has depended almost entirely on clinical features. Thus, Günther divided the disease into acute, chronic, and congenital forms, the acute being characterized by episodes of abdominal and/or nervous manifestations; the chronic, by late appearance of photosensitivity with or without abdominal and nervous symptoms, and the congenital by early photosensitivity.[1] Waldenström substituted the term "cutanea tarda" for the chronic form and subdivided the acute cases into several types, solely on the basis of clinical features.[2] Micheli's classification was also a clinical one.[3] There has actually been no other basis for classification, owing to the lack of exact information as to the pathogenesis of porphyria and to the site of origin of the porphyrins in the various forms of the disease. The literature contains altogether too few data on the porphyrins of the various tissues to permit any judgment as to whether a fundamental division of the various forms of porphyria is possible on the basis of tissue porphyrin content. Certain striking differences in the clinical forms of the disease however, have suggested a fundamental variation in the mode, and quite possibly in the site, of porphyrin formation. Thus, in the acute form large amounts of the Ehrlich-reacting porphobilinogen and other Ehrlich-negative porphyrin precursors are excreted together with some preformed porphyrin. On the other hand, porphobilinogen has not been encountered in the urine in cases of porphyria congenita (erythropoietica). This form is characterized by photosensitivity and, frequently, by enlargement of the spleen and hemolytic anemia. Patients with the latter form excrete mainly uroporphyrin I rather than the Waldenström type of uroporphyrin complex, which is found in acute porphyria and also in the chronic or "cutanea tarda" type of the disease. This complex includes Type I and III isomers, but there is disagreement as to their exact character and proportion. This is discussed in more detail elsewhere.* In the

Presented in part before the Central Society for Clinical Research, Chicago, Nov. 2, 1951.

From the Department of Medicine, University of Minnesota Medical School and Hospital.

This study was supported in part under a contract from the Office of the Surgeon General, United States Army, under the sponsorship of the Commission on Liver Disease, Armed Forces Epidemiological Board. It was aided also by grants from the Atomic Energy Commission, contracts AT (11-1)-100 and AT (11-1)-108.

* References 4, 5, 28, and 35.

"congenital" form nearly all the porphyrin excreted is preformed rather than chromogen or precursor; furthermore, it is largely excreted as free porphyrin rather than as zinc complex, which characterizes the urine in the intermittent acute cases.

The extensive study of the famous case Petry, by Borst and Königsdörffer,[6] provided certain important information about the tissue porphyrins in one type of the disease. This patient had suffered from congenital photosensitive porphyria for all of his 40 years and, as a consequence of porphyrinemia over such a long period, exhibited great excesses of porphyrin in almost all tissues studied. It was evident, both in the reports of Borst and Königsdörffer[6] and in those of Fischer and his associates,[7] that deposition of uroporphyrin I and coproporphyrin I had been so extensive throughout Petry's body that an accurate judgment as to site of origin was indeed difficult, if not impossible. Nevertheless, Borst and Königsdörffer emphasized that the nucleated erythrocytes of the bone marrow were unusually rich in porphyrin. They spoke of these cells as megaloblasts and believed, in fact, that Petry died of pernicious anemia. In retrospect, both from the standpoint of their illustrations, which suggest that the porphyrin-containing cells were normoblasts or erythroblasts, and from other facts about the disease which have subsequently come into sharper focus, as will be noted presently, it seems not unlikely that the anemia, splenomegaly, and hyperplastic bone marrow were part of a chronic hemolytic anemia, a condition often, and probably sooner or later always, observed in this form of porphyria. Within the past four years we have had the opportunity to study two cases of this type in considerable detail. Both were in young girls, one 4 and one 6 years old, with hemolytic anemia and splenomegaly. Splenectomy, liver biopsy, and repeated bone marrow biopsies were carried out in both, and all these tissues were subjected to qualitative and, in part, quantitative porphyrin analysis. The first of these cases has been described elsewhere[8]; the chemical findings in the second will be given in detail in the present communication. For the moment, it will suffice to say that in both instances the bone marrow contained large amounts of uroporphyrin and coproporphyrin, while the amounts in the liver were relatively small. A number of years prior to these observations one of us (C. J. W.) had studied at autopsy a case of porphyria associated with advanced hepatic cirrhosis.[9] In this instance, even though the methods in use at that time were relatively crude, it was evident that the liver contained large amounts of a uroporphyrin-zinc complex, while only traces were demonstrable in the bone marrow. It was not until later that the full significance of this observation became apparent. It was not, in fact, until the liver and bone marrow in the two above-mentioned congenital cases and in several instances of the intermittent acute and of the "cutanea tarda" or "mixed" types had been studied that the concept of two fundamentally different porphyrias became relatively clear. A basic classification was then suggested,[10] now modified slightly as follows:

1. Porphyria erythropoietica—congenital photosensitive porphyria, usually associated with hemolytic anemia and splenomegaly
2. Porphyria hepatica—hepatic disease or functional impairment frequent
   (*a*) Intermittent acute type—abdominal and/or nervous manifestations
   (*b*) "Cutanea tarda" type—late appearance of photosensitivity without other manifestations
   (*c*) "Mixed" type—photosensitivity with intermittent abdominal and/or nervous manifestations.

We have subsequently studied a number of additional cases with respect to bone marrow and liver porphyrin content, comparing these findings with the data for urinary, fecal, and blood porphyrin content. The purpose of the present communication is to present these results and consider them in relation to the above classification.

MATERIAL AND METHODS

During a 15-year period 153 cases of porphyria of various types have been studied in more or less detail. The majority of these were observed in Minneapolis, some few, however, being studied solely on the basis of protocols and urine samples supplied by physicians in other cities. The entire series also included 26 patients with the latent type, all being relatives of patients with manifest disease. Suitable methods for tissue porphyrin assay and fluorescence microscopy have been available only during the past four years. This and other factors have limited the material of the present study to 31 cases. These include 2 of erythropoietic (congenital) photosensitive type with hemolytic disease and 29 of hepatic type of which 11 were the intermittent acute, 13 the "cutanea tarda," and 3 the "mixed" variety; 2 patients had a latent form of hepatic porphyria. Essential clinical and laboratory data are given in Table 1.

The bone marrow and liver were each examined 31 times, 27 times by means of biopsy and 4 times at necropsy. In two of the patients permission was not granted for liver biopsy. In two patients (Cases 42 and 86) two separate studies were carried out; in Case 86 one was done in October, 1950, at which time the patient presented the symptoms of "mixed" porphyria with moderate photosensitivity and abdominal pain, and another was made in June, 1951, when the patient had no evidence of photosensitivity but presented marked abdominal pain and nervous manifestations. While it would have been desirable from a purely scientific standpoint to study the tissue porphyrin content in patients with the intermittent acute type of the disease during an attack, this was not believed justified in many instances, from the standpoint of the patient's welfare. Thus the bone marrow and liver biopsies were carried out at various intervals after convalescence from an acute attack had commenced. Little or no exacerbation was noted after liver biopsy with the exception of one case in which a mild, brief recurrence of pain was observed, but in this instance the patient was inadvertently given a barbiturate prior to a surgical liver biopsy.† These biopsies were regularly carried out under local anesthesia, preoperative medication consisting of 50 mg. meperidine (Demerol) hydrochloride.

Splenectomy was done in the two cases of erythropoietic (congenital, photosensitive) type, and in both the fresh spleen was available for porphyrin studies. The studies of the first of these cases (Case 71) have been published previously,[8] and those of the second case (Case 76) will now be given.

CASE 76.—M. H., a girl, was 4 years 4 months old at the time of her first admission to University of Minnesota Hospitals, Nov. 7, 1950.

History of Present Illness.—During the summer of 1949, when the patient was 3 years of age, several bullous eruptions developed on the face and the back of the hands. At the same time, the excretion of pink to port-wine-colored urine was noted. By September, 1949, the vesicular lesions on the parts of the skin exposed to light had become more numerous, many of them becoming secondarily infected and showing a tendency to heal poorly. During the winter of 1949-1950 the cutaneous eruptions healed almost entirely, leaving slightly depressed scars, and the urine exhibited a pink color only intermittently. With the reappearance of the cutaneous symptoms and darker urine in May, 1950, the diagnosis of porphyria was suggested by Dr. J. B. Burns, of New York, and was subsequently proved by the demonstration of large amounts of uroporphyrin in the urine.

In the summer of 1950, the girl was hospitalized at the Johns Hopkins Hospital, in Baltimore, where an intensive course of parenteral liver therapy was instituted. This was believed to have resulted in a temporary decrease in cutaneous photosensitivity as well as urinary porphyrin

† Drs. Richard Varco, Clarence Dennis, and C. Walton Lillehei, University of Minnesota Hospitals, and Dr. Joseph Garamella, Minneapolis Veterans Administration Hospital, performed the surgical biopsies.

TABLE 1.—*Clinical and Laboratory Findings of Patients Studied*

Case	Initial	Age, Yr.	Sex	Age of Onset of Symptoms	Photosensitivity	Abdominal Pain	Nervous Manifestations	Liver Function Tests * BSP, %	SB 1 Min.	SB T	UU, Mg./24 Hr.	CC	TT	CE	SP, Gm./100 Cc. A	SP, Gm./100 Cc. G	Liver Morphology	Comment	Case
71	D. H.	4	F	2	Marked	0	0	..	0.1	1.0	...	..	..	....	4.3	2.7	Normal	Hemolytic anemia and splemogaly; normoblastic hyperplasia of bone marrow; hirsutism	71
76	M. H.	6	F	3	Marked	0	0	..	...	0.8	...	0	1	....	4.6	2.0	Normal		76
42*a*	B. R.	29	F	23	0	Marked	Moderate	..	0.2	0.6	...	3+	8	0.98	3.4	4.6	Normal	Onset after sulfonamide therapy; 6/52	42*a*
42*b*	B. R.	29	F	23	0	Marked	Moderate	2	...	...	...	3+	4	....	...	...	Normal	11/52	42*b*
66	C. K.	60	M	45	0	Moderate	Slight	9	0.2	1.0	...	0	2	....	3.5	3.7	Normal	Hypertension, cardiac failure; nitrogen retention	66
90	R. T.	35	F	35	0	Moderate	Marked	6	...	...	...	..	4	....	3.0	3.6	Normal	Sister of M. J. (Case 91); brother of patient died of porphyria	90
91	M. J.	30	F	29	0	Moderate	Marked	..	0.2	0.4	...	4	3	....	3.7	4.1	.....	Sister of R. T. (Case 90); attack precipitated by barbiturate	91
92	D. S.	31	M	30	0	Marked	Marked	..	...	...	...	0	..	....	...	...	Normal	Previous convulsions and coma	92
117	L. C.	24	M	23	0	Marked	Severe	4	...	...	...	0	..	....	...	...	Normal	Comatose for 2 wk.	117
138	C. G.	23	F	23	0	Marked	Severe	31	0.5	1.0	...	0	3	0.91	2.6	3.5	Normal	Transient quadriplegia	138
145	R. N.	26	F	25	0	Moderate	Slight	15	0.0	0.4	0.7	3+	4	0.69	...	...	Normal	In remission at time of study	145
137	M. E.	67	F	..	0	0	0	1	...	...	...	2+	4	0.33	3.0	4.0	"Chronic hepatitis"	No symptoms at any time; mother of a patient with acute porphyria	137
141	M. T.	47	F	..	0	0	0	..	0.1	0.5	...	0	2	0.86	...	...	Normal	No symptoms at any time; mother of a patient with acute porphyria (Case 138)	141
83	E. M.	40	F	39	Moderate	0	0	..	0.1	0.7	0.6	1+	2	....	3.5	3.8	Normal	Asymptomatic if protected from light	83
84	M. D.	27	M	22	Moderate	0	0	10	0.2	0.9	...	1+	3	....	5.0	2.3	Normal	Syphilis treated 1945; Wassermann reaction negative	84
87	C. B.	51	M	49	Moderate	0	0	20	0.2	1.3	3.2	0	3	....	3.3	3.2	Fatty met.	Asymptomatic if protected from light	87
103	M. C.	66	F	64	Moderate	0	0	..	0.2	1.4	...	1+	6	....	2.9	4.3	Early cirr.	Sister of H. O'K. (Case 1)	103
105	A. B.	54	M	52	Moderate	0	0	..	0.3	0.8	...	4+	20	0.20	2.1	6.2	Early cirr.	Alcoholic; silicotuberculosis	105
106	H. C.	67	M	57	Moderate	0	0	4	...	...	...	2+	4	0.22	...	...	.....	Diabetes	106
115	E. E.	56	M	56	Marked	0	0	..	0.1	1.2	...	0	3	....	3.1	4.2	Normal	Onset while vacationing in Florida	115
118	J. G.	44	M	43	Slight	0	0	21	0.2	1.1	5.2	0	5	0.81	4.0	3.6	Fatty met.	Alcoholic	118
119	A. M.	27	M	5	Marked	0	0	16	0.1	0.5	...	0	..	....	...	...	Normal	Atypical skin lesions; active pulmonary TB	119
123	E. H.	61	M	53	Moderate	0	0	16	0.2	0.9	2.1	0	1	....	2.8	4.2	Cirrhosis	Diabetes	123
143	J. C.	53	F	53	Marked	0	0	10	0.4	0.6	...	2+	4	0.75	3.4	4.3	Normal	Pernicious anemia in remission	143
144	J. B.	66	M	63	Moderate	0	0	7	...	...	...	3+	6	....	3.2	2.9	Normal	Complete remission in winter	144
148	F. K.	45	M	42	Moderate	0	0	4	0.2	0.8	...	2+	5	0.71	3.4	3.2	Fatty met.	Moderate alcohol intake	148
86*a*	S. R.	48	M	47	Moderate	Moderate	Slight	34	0.5	1.5	...	0	3	....	2.7	3.3	Normal	Findings in 10/50	86*a*
86*b*	S. R.	49	M	47	0	Marked	Slight	..	...	...	...	..	..	....	...	...	Normal	Findings in 6/51	86*b*
127	D. P.	54	M	46	Marked	Moderate	Moderate	6.4	0.2	0.6	13.5	0	4.6	....	...	...	Early cirr.	Scarring of face; muscular atrophy; severe abdominal attacks in past	127
55	L. M.	27	F	22	0	Marked	Severe	..	0.3	1.2	...	4+	1	0.37	3.3	2.7	Normal	Autopsy; respiratory paralysis	55
60	G. S.	17	F	17	0	Marked	Severe	..	0.7	1.2	...	1+	3	....	3.7	3.6	Normal	Autopsy; respiratory paralysis	60
149	R. K.	21	F	21	0	Marked	Severe	..	0.3	0.5	...	3+	1	....	1.7	3.3	Normal	Autopsy; respiratory paralysis	149
1	H. O'K.	50	F	50	Mild	Moderate	Slight	..	...	...	2.2		Icterus index 56				Cirrhosis	Autopsy; sister of M. C. (Case 103)	1

* Abbreviations are as follows: BSP, %, sulfobromophthalein (Bromsulfalein) retention at 45 minutes after 5 mg. per kilogram.[11] SB, serum bilirubin, prompt direct-reacting (1 minute) and total (T).[12] UU, urine urobilinogen.[13] CC, cephalin-cholesterol flocculation.[14] TT, thymol turbidity, in MacLagan units.[15] CE, choline esterase, in Δ pH.[16] SP, serum protein, albumin and globulin (References 17, 18, and 19).

excretion. After the liver injections were discontinued, in September, crops of bullous eruptions reappeared on the face and on the backs of the hands. The patient was then referred to us by Dr. Burns.

Family History.—The child was adopted, and the family history is not known, except that she is believed to be of English parentage.

Past History.—Spontaneous delivery on July 15, 1946. Birth weight, 5 lb., 6 oz. (2,440 gm.). Pyelitis at age of 1 year. Measles at age of 3 years.

Physical Findings on Admission.—First Hospital Admission (Nov. 7-11, 1950): Weight 19.3 kg., temperature 99.2 F. (rectal); pulse rate 90; respiration rate 20; B. P. 104/78. Well-developed well-nourished white girl of stated age.

Skin. Pale, with moderate hypertrichosis of face and extremities. Many small vesicular and vacciniform eruptions on face, forearms, and lower legs, some of them in various stages of healing. Numerous small, slightly depressed, and at times depigmented cutaneous scars on face and dorsum of both hands. No discoloration of teeth (erythrodontia). Several pea-sized lymph nodes in cervical, axillary, and inguinal regions.

Abdomen. Liver palpable at right costal margin. Spleen palpable 3 cm. below left costal margin on deep inspiration.

Laboratory Findings. Routine urine examination negative. Hb 14.0 gm.; RBC 4,570,000; hematocrit 32%; reticulocyte counts varying from 0.7 to 3.1%; WBC 4,650. Differential count: polymorphonuclear cells 51%, lymphocytes 43%, monocytes 3%, eosinophiles 2%, and basophiles 1%. Fractional serum bilirubin: one minute prompt direct-reacting 0.03 mg., total 0.34 mg. per 100 cc. Bone marrow biopsy: hyperplastic marrow, with normoblastic hyperplasia.

Second Hospital Admission (March 27-May 17, 1951): Physical findings essentially unchanged except for marked decrease in number and severity of active skin lesions. Hb ranging from 10.8 to 12.3 gm. Reticulocyte counts ranging from 3.3 to 6.2% (six determinations). Fecal urobilinogen determinations varying from 402 to 520 mg. per 100 gm. (seven determinations). Cold agglutinins, no titer. Coomb's test (direct and indirect) negative. Erythrocyte osmotic fragility normal. Urinary 17-ketosteroids 1.95 mg. per 24 hours. Urinary corticoids 0.3 mg. per 24 hours. Bone marrow biopsy: normoblastic hyperplasia. The patient contracted mumps during this hospitalization and upon recovery was exposed to chickenpox. She was discharged from the hospital and readmitted on June 20, 1951, for splenectomy.

Third Hospital Admission (June 20-July 2, 1951): Physical status unchanged. Hb 10.9 gm. Reticulocyte counts 4.6 and 6.4%. WBC 4,600; polymorphonuclear cells 71%, lymphocytes 27%, monocytes 2%. Splenectomy was performed on June 21, without difficulty. A liver biopsy specimen was taken at the same time, revealing histologically normal liver tissue. The spleen weighed 250 gm. and was histologically normal. The postoperative course was uneventful, and the patient was discharged July 2, 1951.

Fourth Hospital Admission (Oct. 4-Oct. 6, 1951): Since splenectomy, the girl and her parents have noticed a considerable improvement in her photosensitivity, only occasional bullous lesions occurring on the back of her fingers and hands after sun exposure. No change has occurred in the degree of hypertrichosis. Hb 11.4 and 12.5 gm. Bone marrow biopsy: probably normoplastic marrow, with evidence of pathological red cell regeneration; relative lymphocytosis of bone marrow and peripheral blood. Reticulocyte counts: 0.9 and 1.2%. Fecal urobilinogen normal (96 Ehrlich units per 100 gm.)

Follow-Up to June 20, 1953: The improvement in photosensitivity continues, although occasional blisters have appeared intermittently, particularly on the hands. They show a tendency to heal poorly, but they rarely exhibit secondary infection. The girl is able to play outside, although she has been advised to avoid direct sun exposure as much as possible.

The data of the special studies carried out on this patient are given in Tables 4 and 5.

Spleen was also available from two cases of intermittent acute porphyria studied at necropsy.

The method of examination as to the porphyria content of tissues depended in part on the amount of material available. All tissue samples were examined by fluorescence microscopy (see below). When at least 300 mg. of wet tissue was available, actual extraction and quantitative determination of uroporphyrins, coproporphyrins, and protoporphyrins were carried out. The method employed was as follows:

The wet tissue samples were homogenized and the porphyrins extracted by the method of Schwartz and Wikoff for the erythrocyte porphyrin determination.[20] Aluminum oxide chroma-

tography was used for purification and estimation of uroporphyrin, as described in an earlier publicaiton.[21] Since the available tissue samples were often very small, the extractions were carried out with as little solvent as possible. After the tissue sample was extracted with a mixture of ethyl acetate and glacial acetic acid until the extract no longer showed red fluorescence in ultraviolet light, the residue on the sintered glass filter was immersed for 12 hours in a 19:1 mixture of methyl alcohol and concentrated sulfuric acid. In this way it was often possible to extract additional porphyrin as the methyl ester, which was then saponified and determined quantitatively in the above-described manner. In analyzing bone marrow samples from patients with erythropoietic porphyria, we found that very little uroporphyrin was extracted by the original ethyl acetate-glacial acetic acid mixture, most of it being liberated only by the methyl alcohol-sulfuric acid mixture. On the other hand, most of the uroporphyrin in hepatic and splenic tissue was often readily extracted by ethyl acetate and glacial-acetic acid, and subsequent extraction of the tissue remnants with methyl alcohol-sulfuric acid revealed but relatively little additional porphyrin.

The bone marrow samples were obtained from the sternum by aspirating 1 to 2 ml. of material, which was placed in a graduated heparin-containing centrifuge tube. After preparation of slides for morphological study and fluorescence microscopy, the material was spun down at 1,800 rpm, and the cellular material was employed for porphyrin extraction. It is inevitable that marrow samples prepared in this manner contain various amounts of circulating erythrocytes. No attempt was made, however, to apply a correction factor. As will be seen, the results of the bone marrow analysis in the erythropoietic and the hepatic forms of the disease are of an entirely different order of magnitude; consequently, possible differences relative to circulating red blood cells are insignificant. Whenever possible, two equal samples of the same tissue, whether bone marrow, liver, or spleen, were analyzed for porphyrin, one fresh and one after heating, the latter being necessary for the conversion of colorless chromogen or precursor to uroporphyrin. It will be evident in the following that the determination after heating has provided information of much significance. The method of heating the tissue was as follows: An equal volume of isotonic sodium chloride solution was added to the ground tissue in a porcelain dish and the mixture was slightly acidified with acetic acid (red to Congo and litmus papers). After being covered to prevent evaporation, the dish was placed in a boiling water bath for approximately 15 minutes. The optimum period of heating is not exactly known, and it is recognized that it may differ under various circumstances. Some preliminary observations suggest, however, that it is usually in the neighborhood of 15 minutes.

An actual quantitative determination of the porphyrin in the liver was possible only in those instances in which surgical biopsy was performed. The material obtained by needle biopsy was inadequate for this but readily sufficed for fluorescence microscopy. The apparatus employed for this purpose consists essentially of an especially constructed microfluorospectrometer, a part of which is a Steinheil microanalytical spectroscope, such as used by Borst and Königsdörffer in their study of porphyria.[6] The entire apparatus will be described in detail elsewhere. In employing fluorescence microscopy it has been most revealing to study unstained cells first, with respect to intensity and location of fluorescence, and then to observe and identify the same cells after appropriate staining.

For fluorescence microscopy fresh, unstained bone marrow smears or supravital preparations in isotonic sodium citrate solution were used, as recommended by Seggel.[22] Frozen sections were prepared from fresh liver and spleen, or the specimens were fixed in 10% formalin for one hour and then imbedded in paraffin. The unstained sections were then employed for fluorescence microscopy, without removal of the paraffin. Experience thus far indicates that either method may be advantageous in certain instances.

The total urinary coproporphyrin and isomer ratios were determined by the methods of Schwartz and associates.‡ Cold ether solubility and, whenever possible, crystallization of methyl esters and determination of melting points were also carried out with respect to the proportion of isomers. The uroporphyrin was determined by a modification of the method of Sveinsson and Rimington (23), to be described elsewhere.

‡ References 23 and 24.

TABLE 2.—*Porphyrin Content of Biopsy Material, Erythrocytes, and Urine*

Case	Bone Marrow, γ/100 Ml.				Erythrocytes, γ/100 Ml.				Liver, γ/100 Gm.				Urine			Clinical Status at Time of Examination
	Uro-	Copro-	Proto-	Fl *	Uro-	Copro-	Proto-	Fl *	Uro- †	Copro-	Proto-	Fl *	γ/24 Hr. Uro-	γ/24 Hr. Copro-	E. U.‡/24 Hr. Porphobilinogen	
71	..	....	..	Very intense	‡	145	233	Intense	....	....	....	Minimal	75,600	11,200	0	Marked photosensitivity
76	2,492	614	190	Very intense	380	90	42	Intense	870	430	45	Minimal	30,800	5,560	0	Moderate photosensitivity
42*a*	0	Trace	18	0	0	1.7	40	0	133	Trace	55	0	3,480	222	16	Recovering from severe attack
42*b*	..	....	..	0	0	0.8	54	0	187	....	....	0	4,160	366	22	Mild abdominal pain
66	0	0.8	78	0	0	3.4	48	0	804	18	31	Minimal	35,500	463	76	Mild abdominal pain
90	0	1.1	100	0	0	1.2	41	0	§	50	11	0	7,120	206	36	Recovering from moderate attack
91	0	3.1	40	0	0	0.7	39	0	....	....	....	.....	31,320	258	49	Recovering from severe attack
92	0	1.1	47	0	0	0.4	19	0	445	42	47	0	63,000	1,391	200	Recovering from moderate attack
117	Trace	Trace	21	0	11.2	1.7	43	0	410	18	48	0	66,300	270	34	Recovering from severe attack
138	Trace	Trace	15	0	0	4.3	50	0	1,604	Trace	71	0	15,180	134	20	Recovering from severe attack
145	Trace	Trace	42	0	0	0.8	31	0	296	Trace	Trace	Minimal	12,240	186	19	In remission
137	0	Trace	22	0	0	0.6	29	0	143	7	26	0	857	1,138	5	No symptoms
141	0	Trace	25	0	0	0.7	29	0	24	Trace	Trace	0	2,700	332	14	No symptoms
83	..	....	..	0	0	1.0	44	0	....	....	‖	Very intense	3,280	589	0	In remission
84	0	3.0	51	0	0	3.0	50	0	....	....	‖	Very intense	4,410	175	0	In remission
87	0	2.4	47	0	0	0.3	13	0	....	....	‖	Very intense	3,990	960	0	In remission
103	0	16	59	0	0	2.9	58	0	2,950	38	49	Very intense	7,320	422	0	Mild photosensitivity
105	0	Trace	18	0	0	0.4	26	0	10,900	1,340	1,650	Very intense	2,560	1,116	0	Mild photosensitivity
106	0	6.0	17	0	0	1.0	17	0	....	....	....	.....	5,130	1,000	0	Mild photosensitivity
115	0	Trace	24	0	Trace	0.8	23	0	12,000	600	14,900	Very intense	19,200	613	0	Marked photosensitivity
118	Trace	Trace	14	0	0	1.0	34	0	3,360	270	464	Very intense	5,290	585	0	In remission
119	Trace	Trace	18	0	0	0.7	55	0	17.2	Trace	Trace	0	230	468	0	In remission
123	0	1.3	70	0	0	0.9	41	0	....	....	‖	Very intense	9,160	600	0	Mild photosensitivity
143	0	Trace	10	0	0	0.8	32	0	20,900	34	810	Very intense	13,270	838	0	Moderate photosensitivity
144	0	12	39	0	0	1.0	21	0	78,150	5,343	3,471	Very intense	8,400	420	0	Moderate photosensitivity
148	0	5.9	19	0	0	0.5	29	0	53,103	3,878	4,086	Very intense	11,500	925	0	Moderate photosensitivity
86*a*	0	5.1	194	0	0	5.0	38	0	....	....	‖	Mod. intense	3,750	1,033	67	Moderate photosensitivity, moderate abdominal pain
86*b*	0	2.5	148	0	0	3.0	45	0	528	18	82	0	24,540	520	67	No photosensitivity, marked abdominal pain
127	Trace	18	62	0	Trace	9.5	41	0	34,250	407	1,685	Very intense	19,050	359	0¶	Mild abdominal pain, marked photosensitivity

* Fluorescence microscope examination for red fluorescence.
† Uroporphyrin values are those obtained after heating, except for Cases 83 through 148 and Case 127.
‡ Large amounts of porphyrin were present, but a suitable quantitative method was not available at the time this case was studied; uroporphyrin I was crystallized.[8]
§ Liver specimen not analyzed after heating.
‖ Needle biopsy specimen only.
¶ Porphobilinogen has been found at times of severe abdominal pain.
‡ E. U. = Ehrlich units.[26]

TABLE 3.—*Autopsy Findings in Four Patients with Porphyria*

Case	Bone Marrow Porphyrin, γ/100 Ml.			Erythrocyte Porphyrin, γ/100 Ml.			Plasma Porphyrin, γ/100 Ml.			Liver				Spleen Porphyrin, γ/100 Gm.			Urine		
										Porphyrin, γ/100 Gm.							Porphyrin, γ/24 Hr.		
	Uro-	Copro-	Proto-	Uro-	Copro-	Proto-	Uro-	Copro-	Proto-	Uro-	Copro-	Proto-	Porphobilinogen	Uro-	Copro-	Proto-	Uro-	Copro-	Porphobilinogen, E. U./24 Hr.
55	Trace	7.4	106	21.0	1.9	25.0	6.5	1.7	0	131	52	48	Present	105	5.7	25.0	31,000	1,000	80
60	.....	...	...	....	...	....	236	108	0*	3,390	341	123†	Present	...	...	....	45,000	620	27
149	0	Trace	42.5	0	1.9	34	8.9	22	8.4	735	23	281	Present	trace	31.0	85.2	174,720	1,015	115
1	Trace	0	0	Trace	0	+	...	...	..	++++	0	0	.....‡	+	0	0	++++	+	..‡

* Porphobilinogen demonstrated in serum.

† Estimation of porphyrins was carried out after the liver had been kept in the deep freeze for 18 months.

‡ At the time this patient was studied, the significance and method of detection of porphobilinogen had not yet been recognized

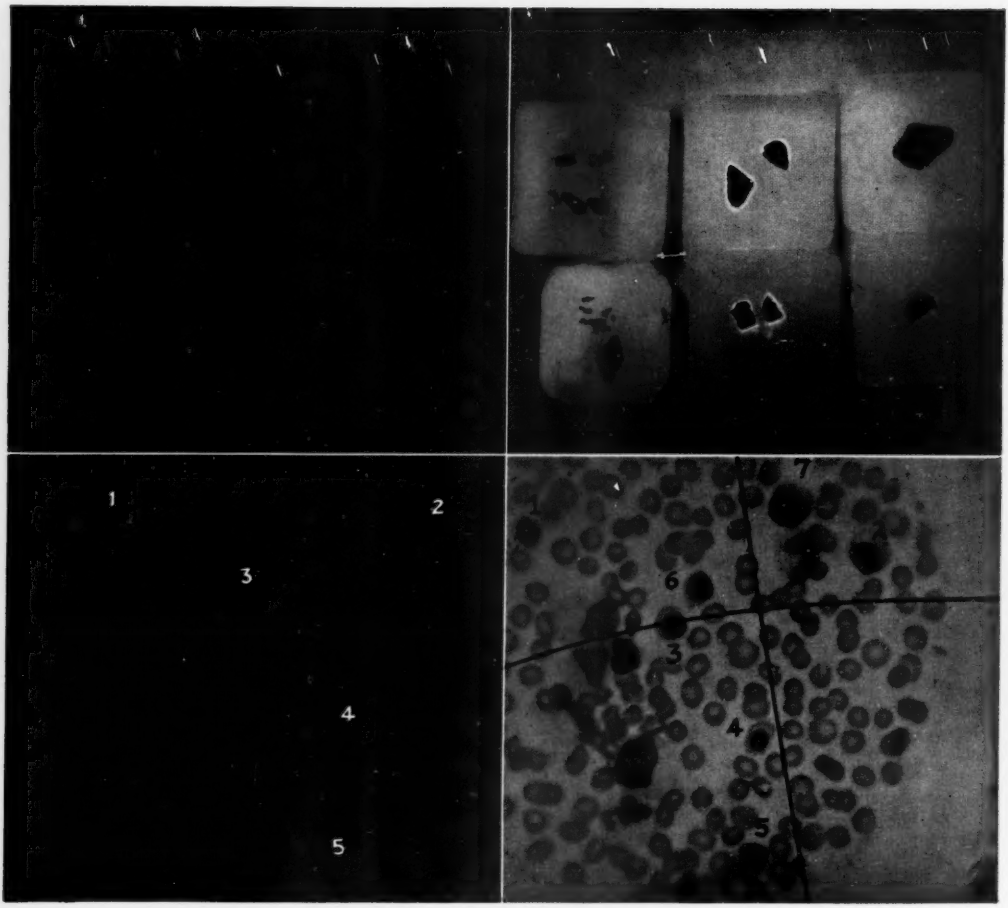

Fig. 1.—(*a*) Upper left, unstained bone marrow in Case 76 (erythropoietic porphyria) in fluorescence microscopy, showing porphyrin-laden normoblasts and immature erythrocytes; × 260. In this and the following figures a Wratten C filter was used as a secondary filter. (*b*) Upper right, paraffin blocks of liver biopsies from six cases of porphyria. In the upper row, from left to right, Cases 76, 148, and 92; in the lower row, left to right, Cases 71, 143, and 66. Cases 66 and 92 were of intermittent acute type, Cases 143 and 148 of cutanea tarda type, Cases 71 and 76 of erythropoietic type. (*c*) Lower left, unstained bone marrow in Case 76 (erythropoietic porphyria) photographed in the fluorescence microscope on color-positive film; × 550. Because of the unsatisfactory nature of the color transparency, the color positive was transferred to black and white and from that a Flexichrome print was made. The greater fluorescence intensity of the normoblastic nuclei is seen. Normoblasts *1* to *5* may be compared with the corresponding cells in the next illustration. (*d*) Lower right, same as preceding illustration. Wright's stain; × 550. Normoblasts *1* to *5* are the same as in preceding. Normoblasts *6* and *7* were nonfluorescing in preceding.

RESULTS

The essential data are summarized in Tables 2, 3, and 4. The following amplification of this data is also desirable:

A. Erythropoietic Cases.—Many of the findings in Case 71 have been reported elsewhere.[8] This report included description of the isolation of uroporphyrin and coproporphyrin I from the urine and observation of porphyrin-laden normoblasts in the bone marrow (Fig. 1*a*). At the time of this earlier study methods of assay for bone marrow and liver biopsy material were not available. In Case 76 the qualitative observations were entirely similar, and, again, uroporphyrin I was isolated from the circulating erythrocytes. About 5% of the latter exhibited red fluorescence in the fluorescence microscope. On staining with Wright's stain these were seen to be polychromatophilic cells. Further study of the bone marrow porphyrin fluorescence in Case 71 and the present investigation of Case 76 revealed that the orthochromatophilic and polychromatophilic normoblasts showed the most intense fluorescence;

TABLE 4.—*Porphyrin Concentrations* in Erythrocytes, Bone Marrow, and Urine in Case 76 Before and After Splenectomy†*

	γ/100 Ml.						γ/24 Hr.	
Date	EUP	ECP	EP	BMUP	BMCP	BMP	UUP	UCP
11/ 9/50	11.0	5.6	55.0	2,635	302	124	8,450	2,280
4/ 2/51	380	90	42.0	2,492	614	190	21,500	3,450
	390	93	45.0	.....	...	...	.....	.....
	362	90	46.0	.....	...	...	.....	.....
6/21/51	440	150	105	.....	...	...	52,300	2,800
Splenectomy 6/21/51								
7/ 3/51	.....	....	....	.....	...	...	1,200	400
9/ 3/51	.....	....	....	.....	...	...	3,100	700
10/ 6/51	122	20	60	176	84	284	6,972	2,310

* Abbreviations are as follows: E, erythrocytes; BM, bone marrow; U, urine; UP, uroporphyrin; CP, coproporphyrin; P, protoporphyrin.

† Very recently we have had the opportunity to study bone marrow, blood, spleen, and liver in another case of erythropoietic porphyria. The specimens were obtained at the time of splenectomy of the 11-year-old girl. The results were essentially similar to those reported in Tables 2 and 4 except for higher concentrations of preformed uroporphyrin in the liver and in the spleen. The findings were as follows: Bone marrow: intense red fluorescence of approximately half the developing red cells. Erythrocytes: EUP 91 γ, ECP 333 γ, EP 395 γ per 100 ml. Serum: uroporphyrin 60 γ, coproporphyrin 34 γ per 100 ml. Spleen: uroporphyrin 9816 γ (unheated), 5990 γ (heated) per 100 gm. Liver: uroporphyrin 1,440 γ (unheated), 2,220 γ (heated) per 100 gm. Urine: UUP 76,000 γ per 24 hours, UCP 7,600 γ per 24 hours, porphobilinogen absent. Dr. Earle L. Lipton, Department of Pediatrics, University of Illinois College of Medicine, provided the opportunity to study this patient and permission to publish the data. Dr. Lipton and co-workers will report the details of this case in a separate communication.

the pronormoblasts or erythroblasts, very little fluorescence; the basophilic normoblasts, somewhat more. In both cases the fluorescence was always much more intense in the *normoblastic nucleus* than in the cytoplasm (Fig. 2). It is noteworthy that a sizable percentage of the orthochromatophilic and polychromatophilic normoblasts failed to exhibit any porphyrin fluorescence (Fig. 1*c* and *d*). This observation, as well as certain morphological differences between the fluorescing and the non-fluorescing normoblasts, will be discussed in detail in a separate communication.[53]

Ethyl acetate-glacial acetic acid extraction of the bone marrow in Case 76 yielded but a small fraction of the total porphyrin content. On one occasion the ethyl acetate extracted but 78 γ per 100 ml. compared with 2,557 γ per 100 ml. extracted from the residue by methyl alcohol-sulfuric acid. On another occasion the comparable

figures were 367 γ and 2,125 γ per 100 ml. In this connection it seems of significance that the ethyl acetate-glacial acetic mixture left the nuclei largely intact. Uroporphyrin I methyl ester, with a melting point of 284 C., was readily crystallized from the bone marrow in Case 76.

The striking decline in erythrocyte and urinary porphyrin concentration in Case 71, in relation to a complete remission of all symptoms following splenectomy, has been described elsewhere.[8] In Case 76 a similar, though not as dramatic, sequence of events was noted. The patient's preoperative reticulocyte counts ranged from 3.8 to 6.4%, and her postoperative counts from 0.9 to 1.2%. The normoblastic hyperplasia in the bone marrow was markedly diminished after splenectomy. The feces urobilinogen preoperatively was increased, ranging from 402 to 520 mg. per

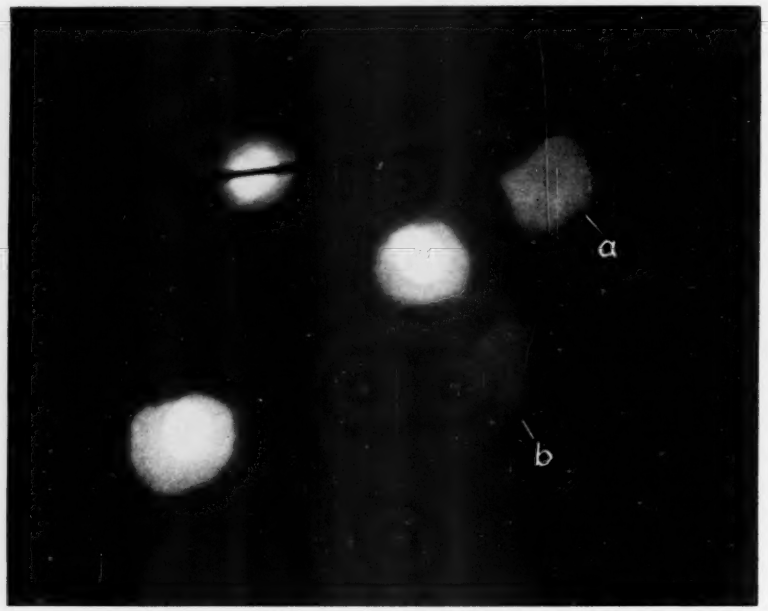

Fig. 2.—Unstained bone marrow in Case 76 photographed in fluorescence microscope with black and white film to show relative intensity of red fluorescence (reproduced in white) in nucleus and cytoplasm of normoblasts; × 1,600. Subsequent staining with Wright's stain showed that cell *a* was markedly and cell *b* moderately polychromatophilic.

100 gm. Postoperatively only one value relating to fecal urobilinogen was obtained, i. e., 96 Ehrlich units per 100 gm. on a random sample, on Oct. 6, 1951. Values for Ehrlich units range somewhat higher than those for milligrams of urobilinogen by the regular quantitative method.[26] This value is therefore markedly reduced as compared with the presplenectomy data. The changes in the erythrocyte, bone marrow, and urinary porphyrins are given in Tables 4 and 5.

In the fluorescence microscope the intensity of red fluorescence in the individual normoblasts after splenectomy (chronological relationship, Table 4) appeared to be unchanged, but the number of fluorescing normoblasts was greatly diminished. This was true in Case 71 as well as in Case 76. It should be noted that in Case 76 no

data after heating bone marrow were obtained, owing to lack of sufficient material for more than one assay. (As already mentioned, the micromethod used was not available at the time Case 71 was studied.)

In Table 4 it is seen that, while the bone marrow uroporphyrin declined markedly after splenectomy, the uroporphyrin of the circulating red cells decreased only moderately and, in fact, was much higher than at the time of the first observation, nearly a year earlier. It is not known whether this interesting difference is related to a change in the erythrocyte release mechanism induced by the splenectomy.

The enlarged spleen removed in Case 71 contained uroporphyrin I, which was readily isolated in crystalline form, as described in an earlier communication.[8] In Case 76 the spleen weighed 250 gm., representing a moderate enlargement for this age. In the fluorescence microscope intense red fluorescence was seen only in the red pulp, the Malpighian corpuscles exhibiting none. The red fluorescence was in the form of fine, dust-like granules and faded in any given field in from two to three minutes of exposure to ultraviolet light. This rapidity of disappearance was surprising, since in the bone marrow the uroporphyrin fluorescence fades much more slowly. Of most significance was the fact that no fluorescence was observed in the nuclei of any cells in the spleen. It was of much interest, however, that about half of the porphyrin was present in the fresh spleen in a nonfluorescing form, the con-

TABLE 5.—*Bone Marrow Findings in Case 76 Before and After Splenectomy*

Date	Myeloid-Erythroid Layer [27]	Normoblasts/100 Nucleated Cells
11/9/50	20%	38
10/5/51	3%	22

centration unheated being 1,740 γ per 100 gm., as compared with 3,415 γ per 100 gm. heated. The possible significance of this observation will be discussed later.

The liver biopsy specimens obtained at time of splenectomy in Cases 71 and 76 exhibited but minimal red fluorescence, in the form of occasional small patchy areas. These did not appear to be within liver cells, though the fluorescence was too weak to be certain, since fading occurred within a few seconds. Nevertheless, appreciable amounts were found in Case 76, in which the method of microassay could be applied. The value for unheated liver was 178.5 γ per 100 gm.; for heated liver, 869.1 γ per 100 gm. The question arose as to whether the liver reduces uroporphyrin to its chromogen or leucocompound, just as sodium amalgam does in vitro. Incubation of uroporphyrin I with normal (rabbit) liver brei has failed to reveal any evidence of reduction. This, of course, does not exclude such a process in normal human liver or human liver in cases of porphyria. The possible significance of the hepatic porphyrin in Case 76 will be considered again in the following.

B. Hepatic Intermittent Acute Type.—As noted in Tables 2 and 3, in none of the 11 cases of this type (Cases 42, 66, 90, 91, 92, 117, 138, and 145, in Table 2; Cases 55, 60, and 149 in Table 3) was there any abnormality of porphyrin content of the bone marrow. In several instances (Cases 66, 86, 91, and 123) part of the marrow was heated without any demonstrable increase of porphyrin. Two cases, however, exhibited significant amounts of uroporphyrin in the circulating red cells (Cases 55 and 117). In neither was there any increase of coproporphyrin or protoporphyrin. It is believed important that the blood serum or plasma in both these

cases also contained significant amounts of uroporphyrin. The possibility is considered that some uroporphyrin was adsorbed on the red cells. In vitro studies of this problem have not been conclusive. Although incubation of normal human blood with uroporphyrin I or Waldenström porphyrin has shown that small amounts of porphyrin are either adsorbed by the red blood cells or are present in the admixed plasma, this porphyrin is readily removed by repeated washing of the cells with isotonic sodium chloride solution. The data in Cases 55 and 117 relate to unwashed cells.

A comparison of liver uroporphyrin values before and after heating is given in Table 6. It is seen that these liver samples contained relatively large amounts of porphyrin precursor, most of the porphyrin appearing only after heating. In Cases 137 and 141, with a latent form of (hepatic) porphyria, the findings were essentially similar to those in the intermittent acute cases, except that the amounts of uropor-

TABLE 6.—*Uroporphyrin Concentration in Liver and Urine Before and After Conversion of Precursors*

Case	Uroporphyrin in Liver, γ/100 Gm. (Wet Weight)		Urine, γ/100 Ml.	
	Before Heating *	After Heating *	Before Heating *	After Heating *
76	178	869	15,150	17,050
42	73	133	270	1,500
66	23	804	32	2,080
92	Trace	445	120	7,840
117	70	410	5,180	32,000
138	...	1,604	113	15,800
137	18	143	595	1,425
103	2,950	540	1,920	2,430
105	10,520	10,900	420	460
115	12,000	...	420	1,360
118	3,360	2,885	.....	.....
86b	31	528	305	3,980
55	47	131	.....	.....
60	1,080	3,390	.....	.....
149	336	735	.....	.....

* Liver brei and urine adjusted to pH 4 to 5 and heated for 15 minutes in boiling water bath.

phyrin and porphobilinogen excreted were considerably smaller. The day following the surgical liver biopsy, however, one of these patients excreted 7,000 γ of uroporphyrin and 27 Ehrlich units of porphobilinogen in 24 hours, but no abdominal or nervous symptoms appeared. Cases 66 and 145 were the only instances in the intermittent acute group in which the liver exhibited definite red fluorescence in the fluorescence microscope, but, as noted in Table 2, this was minimal.

The amount of liver obtained by biopsy did not suffice both for the above analysis and for a test for porphobilinogen. In three of the cases studied at necropsy (Table 3), porphobilinogen was easily demonstrated in the liver, as discussed in section *D*. Certain quantitative data for the spleen will also be considered in this section.

C. Hepatic, "Cutanea Tarda," and "Mixed" Types.—The results in Cases 83, 84, 86, 87, 103, 105, 115, 118, 119, 123, 127, 143, 144, and 148, as shown in Table 2 and Case 1, in Table 3, emphasize the usual occurrence of large amounts of preformed porphyrin in the liver in this group of cases (Fig. 1*b*). In Case 106 determination of liver porphyrin content was not done; this case is included only because

of the normal bone marrow and erythrocyte values. Case 119, in complete clinical remission, was the only exception encountered in which no increase of porphyrin was found by fluorescence microscopy; it was nevertheless possible to determine by extraction that small amounts of uroporphyrin were present in the liver. This patient had rather atypical clinical features, especially in an onset of photosensitivity at the age of 5 years, much earlier than is usual in this group and even belying the designation "cutanea tarda." Nevertheless, it is seen that the bone marrow porphyrin content was entirely normal and that there was no suggestion of hemolytic anemia, as was encountered in Cases 71 and 76, but there was distinct although slight evidence of liver function impairment.

The red fluorescence observed microscopically in the livers in this group was very intense, especially in the polygonal cells, but to a less degree in the von Kupffer cells and still less in the portal connective tissue (Fig. 3 *a* and *b*). It was not uniform in all liver cells, however, some exhibiting it much more strongly than others. The fluorescence was quite stable to ultraviolet light, persisting on continuous exposure up to 15 minutes (this is characteristic of uroporphyrin, in contradistinction to protoporphyrin, which is very labile). In contrast with the findings in the intermittent acute type, it is seen in Table 6 that the liver in this group of cases (Cases 103, 105, and 118) contained much less or perhaps no precursor or chromogen. Although our data relating to this point are admittedly still inadequate, it is evident, both by assay and fluorescence microscopy, that a much greater proportion of preformed uroporphyrin is found in the "cutanea tarda" group than in the intermittent acute cases. Thus far it has not been possible to demonstrate a significant increase on heating the liver in the "cutanea tarda" cases, and, indeed, a moderate decrease is seen in Cases 103 and 118, for which data are available (Table 6). Nevertheless, in Cases 103 and 115 evidence is noted of a precursor in the urine converted to porphyrin by heating (Table 6). The significance of this finding is not clear, especially in relation to the failure to demonstrate precursor in the liver in Case 103, is not clear, also the absence of urinary porphobilinogen in both cases.

In Cases 143, 144, and 148 uroporphyrin has been crystallized from the liver biopsy material. The melting points of the methyl esters were 264 and 268 C., respectively, and decarboxylation to coproporphyrin yielded 42% coproporphyrin III in the first instance, 56% in the second, and 67% in the third, these results being obtained by the fluorescence-quenching method.[24] Nevertheless, coproporphyrin I methyl ester was readily crystallized (melting point 245 to 247 C.) in all three instances. It is noteworthy that decarboxylation of the urinary uroporphyrin isolated from the first two patients at approximately the same time revealed only 14% and 11% isomer Type III, respectively. The significance of this difference remains to be determined. It is possible that there is a differential rate at which the two isomer types leave the liver.

The results in Case 86, in a patient with the "mixed" type of hepatic porphyria, are believed to provide important evidence of a close fundamental relationship of the "intermittent acute," "cutanea tarda," and "mixed" forms of the disease, the latter term simply indicating the presence in a given case, at one time or another, of photosensitivity, as well as abdominal and/or nervous manifestations. In Case 86 at the time of the first liver biopsy (October, 1950) photosensitivity was in the foreground and the patient had only mild abdominal pain. A needle biopsy revealed moderately intense red fluorescence in the fresh, unheated sample. The material was insufficient for quantitative determination. In June, 1951, the clinical picture had

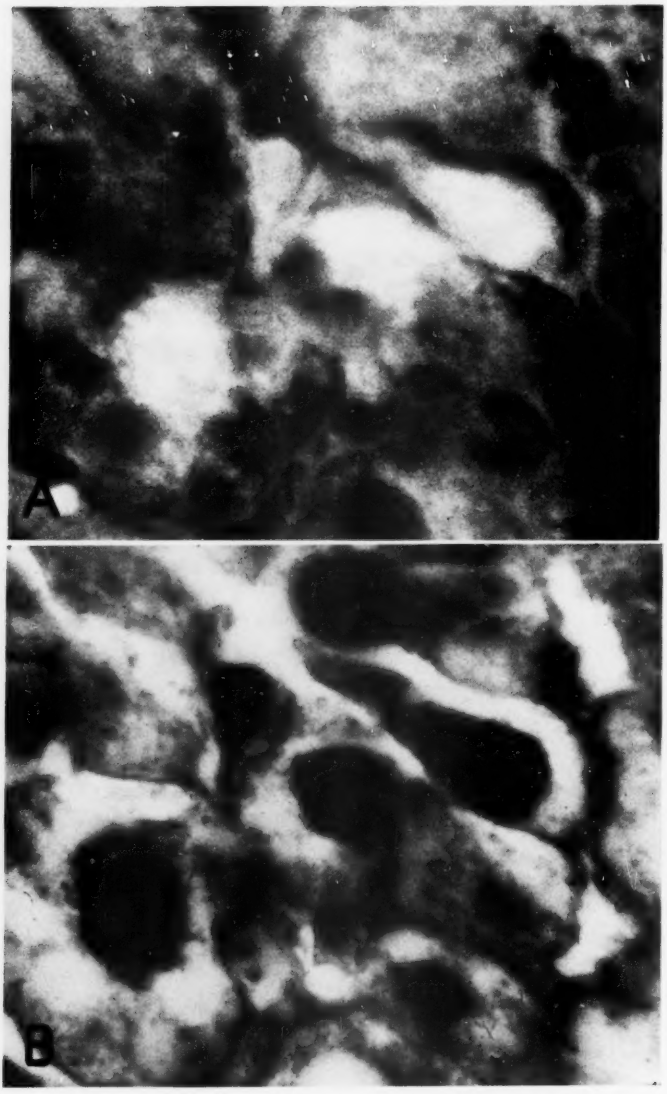

Fig. 3.—(*a*) Unstained frozen section of liver from Case 105, photographed in fluorescence microscope on black and white film (red fluorescence shows in white); × 1,500. (*b*) same area as in *a*, after staining with hematoxylin and eosin. The appearance suggests a greater porphyrin content in the liver cell nuclei.

quite changed, in that the patient no longer had photosensitivity, despite similar sun exposure, the skin lesions having entirely healed, but now abdominal pain and excessive nervousness were prominent. A surgical liver biopsy was done, and the quantitative porphyrin data are given in Tables 2 and 6. Sections of the fresh liver at this time failed to exhibit red fluorescence, which is readily explained by the low porphyrin concentration prior to heating. An increase of about 15-fold is noted after heating, the increase in the urine being of the same order of magnitude (Table 6). Thus it is evident that in the earlier study of this case the findings were mainly those of the "cutanea tarda" group, i. e., prominent photosensitivity and plentiful preformed porphyrin in the fresh liver; in the later study, however, they were those characteristic of the "intermittent acute" form, i. e., abdominal pain and large concentration of porphyrin precursor with relatively little preformed porphyrin in the liver and urine.

D. Cases Studied at Necropsy.—The results in the cases studied at necropsy are of considerable interest. The patients in Cases 55, 60, and 149 died with neuropsychiatric manifestations, all three having quadriparesis, severe hysteroid behavior, and coma. Corticotropin was administered in Cases 55 and 149, but without noticeable benefit, possibly because the patients had been in a semicomatose state for some time before corticotropin therapy was started. The question as to whether corticotropin is beneficial in this disease has been discussed elsewhere.[28] There had been no photosensitivity in any of these three cases. Case 1, however, is believed to have had photosensitivity and to represent a case of "mixed" type. Since the patient was semistuporous from the time of admission, it was never possible to obtain an adequate history. Scarring suggestive of previous photodermatitis was present on the face, neck, and hands. It is interesting that this patient, whose chief problem terminally was abdominal and hepatic, has a sister, Case 103 in the present series (data in Tables 1, 2, and 6), who has only the "cutanea tarda" type of the disease. The significance of this will be discussed. An interval of 13 years elapsed between our study of Case 1, the first case of porphyria studied in this clinic, and the sister, Case 103. The results of the earlier study of this case by one of us [9] are included in Table 3 because even though purely qualitative in character they are nevertheless quite in accord with our more recently acquired quantitative data, as already described and as obtained in Cases 55, 60, and 149. The most complete studies were carried out in Cases 55 and 149. The methods of porphyrin assay used were not available until some time after the necropsy in Case 60, but considerable liver and plasma from this case had been kept in the deep freeze, thus permitting the porphyrin estimations given in Tables 3 and 6.

The liver in Case 1 contained large amounts of zinc-uroporphyrin.[9] The methyl ester was isolated in crystalline form, as described in an earlier paper.[29] This was shown to consist mainly of the Type I isomer.

The data in Cases 55 and 149 clearly reveal a normal bone marrow porphyrin content, as contrasted with the considerable amounts found in the liver. The possible significance of these observations will be discussed later. In Case 55 the fresh spleen contained 2.0 γ per 100 gm. of uroporphyrin, whereas after heating the value increased to 105 γ per 100 gm. In Case 149 only a trace of uroporphyrin was present either before or after heating. The possible significance of these observations will be discussed later.

Various tissues from Cases 55 and 149 were studied by ultraviolet fluorescence microscopy. These included various parts of the brain and spinal cord, paravertebral sympathetic ganglia, adrenals, pituitary, spleen, bone marrow, liver, and kidneys. In Case 55, no significant amounts of porphyrin were observed, with the possible exception of the distal convoluted tubules of the kidney, in which a small amount of red fluoresence was noted. Repeated extractions of brain tissue from this case revealed normal coproporphyrin concentrations, between 1.4 and 1.6 γ per 100 gm.§ No uroporphyrin was found before or after heating. In Case 149 patchy red fluorescence was noted in the hypothalamic region, the fornix, and parts of the brain stem. Certain peripheral nerves, e. g., the sciatic and the abducens nerves, also exhibited patchy red fluorescence. It should be noted that, as a result of increasing experience, the detection of fluorescence in Case 149 is believed to have been more sensitive than in Case 55. It is noteworthy that the fresh (unheated) liver in Case 55 contained 47 γ uroporphyrin per 100 gm. without exhibiting significant microscopic fluorescence. Since this may be due to masking of fluorescence by other materials present in the sections, it is clearly impossible to exclude a significant content of uroporphyrin or precursor on the basis of negative fluorescence microscopy alone.

Porphobilinogen was easily demonstrable in the liver in Cases 55, 60, and 149. The plasma in Case 60 gave a moderately positive Ehrlich reaction and had very high concentrations of porphyrins (Table 3). This patient died of the disease shortly after these studies. The porphobilinogen reaction was not carried out on the liver in Case 1, as its significance was not appreciated at the time of this study. Case 149 was the only one in which a porphobilinogen reaction was carried out with bone marrow homogenate. No porphobilinogen could be demonstrated.

COMMENT

The present study has confirmed and extended recent observations in this laboratory indicating the existence of two fundamentally distinct forms of porphyria: (1) erythropoietic, in which the excessive uroporphyrin and coproporphyrin formation occurs in the developing red blood cells of the bone marrow, and (2) hepatic, in which the liver is regarded as the principal or only site of abnormal porphyrin formation. The latter form is believed to comprise a group including (*a*) the "cutanea tarda" type, in which photosensitivity alone is present, (*b*) the intermittent acute type, characterized by abdominal and/or nervous manifestations, and (*c*) the "mixed" type, in which photosensitivity together with abdominal and/or nervous symptoms occurs in the same case, although not necessarily at the same time. MacGregor and Rimington [30] have recently objected to use of the term "mixed" in designating cases of this type. The case on which their study was based, however, presented a remarkable mixture of photosensitivity with skin lesions, together with well-defined intermittent episodes in which jaundice, abdominal pain, hypertension, retinal arteriolar spasm, and manic behavior were noted. Porphobilinogen was only observed in the urine during the last, and fatal, episode of the disease, but it was not stated whether the tests for porphobilinogen in the earlier attacks were carried out on fresh samples. Our own experience has shown that an initially positive test on a fresh sample may become negative after the urine has stood for as little as 12 to 24 hours. We would regard Rimington's case as one of "hepatic mixed" type according

§ These determinations were carried out by Dr. P. Blanshard.

to the foregoing classification. Use of the term "mixed" appears fully justified for cases in which photosensitivity and skin lesions are combined with abdominal and/or nervous manifestations that are clearly referable to the disease. We have used the term even when the skin lesions are not concurrent in time with the abdominal or nervous symptoms, as in Case 86 of the present series (Tables 1 and 2, and discussed again in the following). The designation "cutanea tarda" is purely clinical, and it is perhaps best to limit use of this term to cases in which the manifestations have been limited to the skin.

Rimington regards the "cutanea tarda" type as an entity, fundamentally distinct from any of the other forms. He believes that the occurrence of relatively large amounts of porphyrin in the feces during remission of the disease, as in the case reported by MacGregor, is a basic feature in separating the "cutanea tarda" form, including what we have designated as the mixed type, from the intermittent acute disease. It should be borne in mind, however, that in the latter cases relatively large amounts of porphyrin may also be excreted in the feces even during remission. We have recently had opportunity to make direct comparison of the fecal porphyrins in typical cases of the "cutanea tarda" and the intermittent acute type, both in complete remission. The data are as follows:

	Coproporphyrin, γ/Day	Uroporphyrin, γ/Day
Cutanea tarda	2,970	1,320
Intermittent acute	2,083	1,103

These differences are hardly significant. What is more important, the abnormal formation of pyrrol compounds in the intermittent acute type is expressed mainly, or to a considerable extent, in the continued elaboration of porphobilinogen, which is not excreted in the bile or feces but only in the urine. We agree that an important fundamental difference exists between the formation of porphobilinogen and other porphyrin precursors in the liver in the acute type versus the formation of preformed porphyrin in the "cutanea tarda" type, but it is evident from the present study that in the same person, as exemplified particularly in Case 86, there may be a change from time to time as to which form of abnormality is represented. Comparison of the data for the liver uroporphyrin content, in Tables 2, 3, and 6, reveals a marked difference between the intermittent acute and the cutanea tarda groups. The concentration in the latter cases as a rule exceeds those in the acute cases, even after the heating. This difference is believed to be due in part to an incomplete conversion of porphobilinogen and other porphyrin precursors in the liver to uroporphyrin during the heating process. Under these circumstances a considerable fraction of the porphobilinogen is undoubtedly converted to porphobilin, not porphyrin.

It seems clear that latent cases may be observed in any form of porphyria, but latency is much more frequent and prolonged in the hepatic type. It does not appear to be necessary to limit the designation of latency to any particular group.

The erythropoietic and the hepatic "'cutanea tarda" types have photosensitivity in common, and from the present observations it seems not unlikely that this is due to relatively high concentrations of uroporphyrin in the body, in the former type stemming from the bone marrow and in the latter, from the liver. Porphobilinogen is not observed in the urine in either of these types, but is regularly found in the "intermittent acute" cases, usually in association with abdominal pain or nervous

manifestations or both. In these the liver contains very little preformed or demonstrable uroporphyrin, but upon heating much larger amounts become evident. Previous studies provide but scant information in this regard. Vannotti [31] refers to one case of acute porphyria in which the liver at necropsy contained surprisingly large amounts of uroporphyin. In the case of Derrien and Benoît [32] only coproporphyrin and protoporphyrin could be demonstrated in the liver, and in Duesberg's and Emminger's case ‖ the only porphyrin encountered was ether-soluble, hence either coproporphyrin or protoporphyrin. Gray [35] emphasized the apparent lack of uroporphyrin in the liver in an acute case, and, interestingly, with relation to the present findings, he contrasted this with the marked excess observed in a "chronic" or "cutanea tarda" case.[36] On the basis of present results, it seems likely that heating the liver homogenate in such instances would permit demonstration of uroporphyrin in large amounts.

Case 86, of "mixed" type, was one of the most instructive of the present cases. During a period of photosensitivity without pain or nervous symptoms the liver obviously contained fairly large amounts of preformed porphyrin; later, without evident photosensitivity but when abdominal pain was prominent, the liver contained very little porphyrin but considerable amounts of precursor. The preponderance of precursor or chromogens, including porphobilinogen, in the intermittent acute cases suggests that one or more of these substances may be responsible for the abdominal and nervous manifestations. Although the view has previously been favored [10] that porphobilinogen or an immediate derivative is more likely to be implicated, other substances may be fully as important, or even more so; indeed, in two of the present cases of the hepatic mixed type porphobilinogen could not be demonstrated in the urine at a time when there was moderate abdominal pain.

Crystalline porphobilinogen has recently been isolated from human acute porphyria urine by Westall.[37] Rimington and co-workers ¶ have described strong evidence that the substance is monopyrrolic in character. Westall's observation that the crystals and their acid solution, on heating, are converted in part to uroporphyrin has readily been confirmed in this laboratory. As previously reported,[10] however, appropriate treatment of acute porphyria urine usually permits preparation of concentrated solutions of porphobilinogen which fail to yield porphyrin on heating at pH 4.0. Also, it has usually been possible to demonstrate an Ehrlich-negative ethyl-acetate-soluble porphyrin precursor in such urines, which is readily converted to porphyrin by ultraviolet radiation. These observations were believed to indicate that porphobilinogen is not a uroporphyrin precursor, but in view of Westall's achievement it is evident that this concept is incorrect, and a study is in progress to determine the significance of the earlier observations. The results of this study will be described separately.

One of the most intriguing observations in the present study, relating to the precursor problem, was that of the porphyrin content of the spleen in Case 55. Essentially all of this was present as some form of precursor or complex first made evident by heating (103 of a total of 105 γ per 100 gm. of spleen). Whether a precursor was formed in the liver and taken up from the circulation by the spleen, whether the spleen had taken up and reduced a circulating porphyrin, or whether the

‖ References 33 and 34.

¶ References 38 and 39.

precursor was actually fabricated in the spleen could not be determined. In contrast with this finding in Case 55, the spleen in Case 149 contained only traces of uroporphyrin, even after heating. The only possible explanation that can be suggested for this difference may lie in the great disparity of duration of the two cases. In Case 55 there had been many attacks over a five-year period and the patient had been in severe relapse for two months and was semicomatose for one month before death. In Case 149 the patient died three weeks after onset of the first attack.

One might question whether porphyrin formation in this type of the disease (above classified as hepatic) is not actually more generalized, perhaps throughout the reticuloendothelial system, or possibly in nerve tissue. The main point against a reticuloendothelial origin is the absence of any increase in the bone marrow of either uroporphyrin or precursor. Formation in the nervous system cannot be excluded, but our findings are similar to those of Klüver,[50] i. e., an unimpressive, patchy, and irregular porphyrinization of small areas. Evidence is presented elsewhere [41] as to the primary role of the liver in a form of experimental porphyria in animals, similar in a number of respects to the human hepatic (acute) type. The experimental form is produced by allylisopropylacetylcarbamide (Sedormid) and is correlated in severity with a striking decrease in hepatic catalase concentration.[42] Studies of hepatic catalase in human cases have been commenced, but as yet no conclusive information has been obtained. It is noteworthy that many of the patients listed in the hepatic porphyria group show evidence of slight to moderate liver function impairment (Table 1). This is particularly true for the late cutaneous cases, in which 6 out of 12 patients were found to have abnormal liver histology. There is a considerable literature relating to hepatic function impairment or histologic changes in cases of acute or cutanea tarda types of porphyria. This has been considered by previous authors.# As seen in Table 1, a number of patients with normal liver histology had evidence of some liver function impairment.

In previous communications we have emphasized the complete absence of urinary porphobilinogen in relation to photosensitivity.* This is confirmed in the present study, as noted particularly in Table 2. It is seen that porphobilinogen was excreted only in the intermittent acute or "mixed" type of the disease, in relation to abdominal or nervous manifestations. In the three fatal cases in which an adequate amount of liver was available for testing, porphobilinogen was readily demonstrated. Prunty [43] also observed and was able to concentrate relatively large amounts of porphobilinogen from the liver in an acute fatal case.

Some additional comment is needed with respect to the remarkable concentrations of uroporphyrin in the bone marrow in the erythropoietic cases, particularly the quantitative data in Case 76. It is seen in Tables 2 and 4 that the amounts of uroporphyrin in the bone marrow and urine were so large, as contrasted with those in the circulating red cells, that a release of porphyrin from intact normoblasts in the marrow is strongly indicated. Simple calculations reveal that in the first preoperative period hemolysis (or breakdown) of about 80 liters of circulating red cells or 350 ml. of packed bone marrow would have been necessary to liberate the amount of porphyrin in the 24-hour urine sample. Although there was a distinct increase in the rate of erythrocyte destruction, these figures, of course, are beyond any reasonable

References 2, 31, 35, and 46.

* References 28 and 29.

possibility, the only alternative being a relatively rapid fabrication and release of porphyrin from the normoblasts during their process of maturation. The fact that some normoblasts exhibited much porphyrin fluorescence and others none, together with certain morphological differences between these cells,[53] suggests the existence of an abnormal and a normal line, and it is quite possible that the former represents the essential constitutional disturbance or inborn error of this disease. The consistent finding, in the fluorescence microscope, of larger amounts of porphyrin in the nuclei of the fluorescing normoblasts is of fundamental significance and will be considered in detail elsewhere.[53] A similar observation in lead poisoning has been reported by Vannotti.[31]

The remarkably beneficial effect of splenectomy in cases of the erythropoietic type (especially our Case 71) raises the question of the essential role of the spleen in this form of porphyria. There is much evidence in the earlier literature that splenomegaly and hemolytic anemia are frequent, if not sooner or later constant, manifestations.† The previous failure to distinguish sharply between the "cutanea tarda," or hepatic photosensitive, and the erythropoietic form has confused this point in the past, as the former type is not characterized by hemolytic anemia. Thus it is quite likely that some cases reported in the past [46] as of the congenital photosensitive (erythropoietic) type actually were hepatic photosensitive, or "cutanea tarda," forms. The available evidence and our experience suggest that the hemolytic process, with its associated splenomegaly, is dependent on a primary abnormality of the developing red cells in the bone marrow. The benefit from splenectomy is readily attributable to the marked reduction in red cell destruction and consequent diminution of compensatory erythropoiesis which results. As the rate of erythropoiesis falls, the output of uroporphyrin by the bone marrow declines sharply, as noted in Table 4. This was true even to a more striking degree in our previous report of the findings in Case 71.[8] Although the remission in this case has now endured for four years, the possibility of a resumption of hemolytic anemia and/or heightened porphyrin formation, with recurrent photosensitivity, is by no means excluded. Gray and Neuberger [47] reported a case of congenital porphyria in which splenectomy was done, without definite benefit. It may be of significance that their case was in a man aged 38, while both of our cases were of female children, 4 and 7 years old. The case of de Marvel and Pons [45] was also of a young girl who was benefited considerably by splenectomy.

The large amounts of porphyrin in the spleen in these cases may well be due simply to accumulation and storage of porphyrins from destroyed erythrocytes. A formation of porphyrin in the spleen itself is not excluded, but it appears less likely. Reference has been made to the finding that considerably more porphyrin was evident after heating as compared with that on extraction of the fresh spleen. Here one must consider that the heat may simply have released bound porphyrin, but it is also possible that a reduction of preformed uroporphyrin had taken place in the spleen. Whether there had been transportation of precursor from the bone marrow to the spleen cannot be determined. It seems not unlikely that the relatively small amount of uroporphyrin in the liver in Case 76 was brought to it in the blood from the bone marrow or spleen or both. An hepatic formation of this porphyrin appears

† References 1, 6, 44, and 45.

much less probable, especially in view of the excessive formation in the bone marrow normoblasts and the striking contrast of other features with the hepatic forms of the disease, as already discussed.

There is little reason to doubt that photosensitivity is related to the marked photodynamic effect of uroporphyrin. The present study clearly indicates that this manifestation is encountered only when preformed porphyrin is readily demonstrable in considerable amount, either in the liver (in the hepatic "cutanea tarda" variety) or in bone marrow and spleen (in the erythropoietic type). We have previously commented on the fact that in the latter form the urinary porphyrin is in the free state, while in the hepatic group it is mainly excreted as a metal complex.‡ Its absorption spectrum is identical with that of uroporphyrin-zinc complex, and the positive identification of zinc in the complex obtained from the liver in Case 1 has been previously reported.§ The question has been raised in the past as to whether the complexing with zinc prevents photosensitivity. While it is true that the zinc complex has less fluorescence intensity than the free porphyrin, it is at least clear that in the "cutanea tarda" group all or nearly all of the porphyrin may be excreted as the zinc complex. Thus, it is doubtful whether this is of any importance, although it is possible that the photosensitivity would be severer were it not for the metal complex formation. The possibility is considered that in the hepatic group the zinc complex is more readily formed because of the relative abundance and availability of zinc in the liver, while in the erythropoietic form the need of zinc for red cell and leucocyte formation in the bone marrow may be responsible for the excretion of free porphyrin rather than zinc complex.

It has been difficult in the past to understand the occurrence of certain families with porphyria in which one member had a photosensitive form of the disease and another abdominal and/or nervous manifestation.‖ The family studied by Calvy [51] is of special interest in this regard. Eight members in three generations presented acute porphyria without photosensitivity, or a mixture of acute and photocutaneous symptoms, or a latent porphyria. We have recently had the opportunity to examine the urine of the son of the patient in Case 127 of our series, the data for the father being given in Table 2. This man presents marked photosensitivity together with mild abdominal pain and weakness of the extremities. The son, however, has at no time had skin lesions and complains mainly of intermittent abdominal pain and nausea. A sample of his urine mailed to us contained 2,345 γ per 100 gm. of uroporphyrin, but the porphobilinogen reaction was negative. The difficulty with respect to such families disappears with the appreciation that photosensitivity occurs as a result of either of two fundamentally different abnormalities, one in the liver, the other in the bone marrow. Thus far, at least, there is no information indicating a familial mixture or crossing of these two quite distinct metabolic errors. The "mixed" type of hepatic porphyria, as best exemplified by Case 86 in the present group, clearly reveals the close fundamental relationship of the intermittent acute and the "cutanea tarda" variety, the chief determinant for the character of symptoms in any given case or given time in the same case appearing to be the ratio of preformed porphyrin to porphyrin precursors in the liver.

‡ References 4 and 29.

§ References 4 and 9.

‖ References 3, 48, 49, 51, and 52.

SUMMARY AND CONCLUSIONS

The porphyrin content of liver and bone marrow has been studied, either by microassay or fluorescence microscopy or both, in a series of 31 cases of porphyria, including 2 of the erythropoietic (congenital, photosensitive) form and 29 of the hepatic group, of which 13 were intermittent acute, 13 were "cutanea tarda," and 3 were "mixed."

The congenital photosensitive form is best designated as erythropoietic, on the basis of abnormal porphyrin formation in relation to the degree and type of normoblastic activity in the bone marrow. The porphyrin formation is believed to emanate largely, if not entirely, from the normoblastic nucleus. Indirect evidence is presented indicating that the uroporphyrin and coproporphyrin of the excreta are liberated from intact developing normoblasts in the bone marrow. The spleens in these cases also contained large amounts of uroporphyrin, probably representing destruction of porphyrin-laden erythrocytes. Splenectomy was followed in both instances by diminished porphyrin excretion and disappearance or great improvement of photosensitivity. This is believed to be related to diminished erythropoiesis in response to the reduced blood destruction.

In the hepatic group the bone marrow porphyrin content was consistently normal, but the amounts of porphyrin or porphyrin precursor in the liver were invariably increased, usually to a very marked extent. In the intermittent acute cases the urine and liver contained the Ehrlich-reacting porphobilinogen but relatively little preformed uroporphyrin. These cases were characterized by abdominal and/or nervous manifestations without photosensitivity. In the photosensitive "cutanea tarda" cases the liver contained chiefly preformed porphyrin with relatively little precursor. In a case of "mixed" type, studied over a long period, chemical and clinical manifestations of the intermittent acute and of the "cutanea tarda" variety have been noted separately, at different times. The cases in the hepatic group often exhibited liver functional impairment or structural change, including cirrhosis.

Technical assistance was given by Barbara Hanson, Marie Kiefer, Mrs. Violet Swenson, Irene Bossenmaier ,and Mary Ann Farisy. The photographs were taken by LeRoy Christenson. Henrietta Broman has assisted with the bone marrow biopsies.

The Department of Pediatrics, University of Minnesota Hospitals, and the Medical Service, Minneapolis Veterans Administration Hospital, have permitted us to study cases on their respective services. Dr. H. Michelson and the staff, Division of Dermatology, University of Minnesota Hospitals, have referred to us for study a number of patients with porphyria cutanea tarda.

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PRESENT CONCEPTS AND TREATMENT OF PLASMODIUM VIVAX MALARIA

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WITHIN the past few years classic concepts of malaria have been modified by the addition of new knowledge. The details on different strains of Plasmodium vivax (benign tertian), discovery of tissue stages of P. vivax and P. falciparum, and discovery of new therapeutic agents have all added to our understanding of malaria and made rational treatment possible. The majority of these changes have come about through controlled tests in human volunteers, following careful preliminary work in animals.

The data on various strains of P. vivax have done much to aid our understanding of the relapse pattern of this type of malaria. Coatney and co-workers* have worked out the life pattern of the St. Elizabeth strain, a temperate zone malaria, and of the Chesson strain, a tropical strain originating in the South Pacific.

The Figure shows the relapse pattern of these two strains of P. vivax malaria in experimentally induced infections. Each attack was treated with quinine.

Patients infected with the Chesson, or tropical, strain and treated with noncurative medication exhibit relapses approximately every two to six weeks without reference to seasons (Fig. B). This type of relapse pattern might be expected to have evolved in a climate where susceptible mosquitoes, as well as the proper humidity and temperature, are available throughout the year.

In contrast, the St. Elizabeth strain, a temperate zone malaria, has a long latent period (Fig. A). In naturally acquired infections this latent period usually corresponds to the winter months. A typical case develops in the summer and is treated. Treatment is followed by a period of latency lasting until about March or April of the succeeding year, when relapses begin. Here again adaptability of the parasite has probably resulted in this pattern. In most of the temperate zone mosquitoes are not available during the winter months for transmission of the disease; therefore the only P. vivax malarias which have survived have been those which developed a period of latency with relapse in the spring, when mosquitoes are available for transmission.

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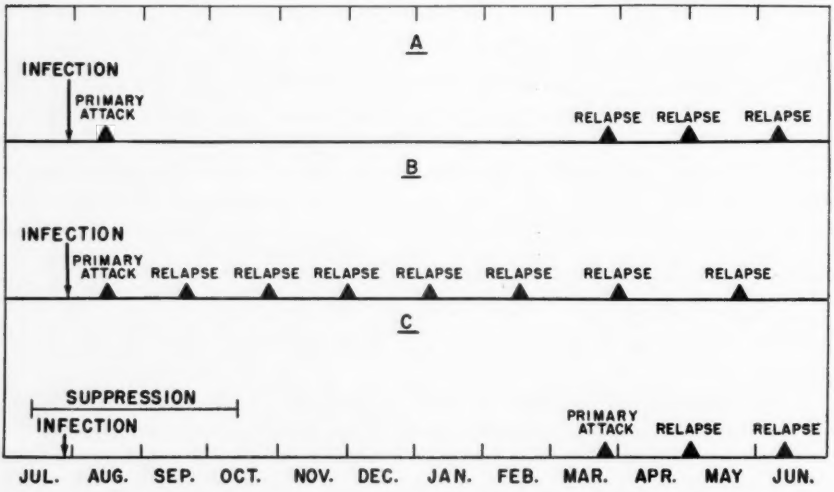
* References 1 and 2.

The relapse pattern of the Korean type of P. vivax malaria is similar to that of the St. Elizabeth strain, according to Alving and co-workers [3] and Hankey and co-workers.[4]

When a mosquito infected with malaria bites a man, the sporozoites remain in the blood stream for approximately 30 minutes, as shown by Fairley.[5] The sporozoites leave the circulating blood and are thought to lodge in the liver, and possibly in the spleen and other parts of the reticuloendothelial system, where they set up the tissue stage (exoerythrocytic) of the disease. After a period of development merozoites are released by the tissue parasites and enter circulating red blood cells to initiate the patent infection. These same tissue parasites are responsible for relapses, which occur when merozoites are released periodically, according to the



Relapse patterns of P. vivax malaria: (*A*) temperate zone pattern; (*B*) tropical zone pattern; (*C*) temperate zone pattern modified by suppression.

type of malaria. The long latent period in temperate zone strains of P. vivax is thought to be due to quiescent tissue parasites.

Shortt and associates † have demonstrated lesions in biopsy sections of human liver following heavy inoculations of P. vivax and P. falciparum sporozoites, and these lesions are considered to be the the exoerythrocytic stages. Jeffery and co-workers [8] have demonstrated similar lesions in a person infected with P. falciparum. Others have shown tissue parasites in microscopic sections from monkeys [9] and birds ‡ infected with malaria.

In P. vivax malaria of the temperate zone type the primary attack is frequently suppressed during the summer months by chloroquine or other suppressive agents, suppressives being discontinued during the winter months. Owing to the long latent period, the primary attack of malaria does not occur until the following

† References 6 and 7.

‡ References 10 and 11.

spring or summer, nine months or more after the initial infection. In rare instances a delayed primary attack may occur even though no suppressive drug has been given. This demonstrates the importance of a history covering the previous summer, as well as the current spring or summer, in cases of P. vivax malaria.

Figure, C, shows the relapse pattern of a temperate zone type of P. vivax as modified by suppression.

The strains of P. vivax cannot be differentiated morphologically. It is not until the relapse pattern is known, in patients treated with noncurative medication, that one can be certain of the type involved.

In P. vivax malaria the tissue stage of the parasite has, in the past, hampered cure of the disease. The common antimalarials, such as quinine, chloroquine (Aralen), quinacrine (Atabrine), or chlorguanide (Paludrine), attack only the blood forms of the P. vivax parasite and have little or no effect on tissue stages. Therefore a patient with P. vivax malaria, treated at each attack with one of these medications, continues to have relapses for upward of two years, in rare cases even longer, unless the patient has or develops enough immunity to shorten the course.

There are some P. vivax infections in which merozoites seem to be released only once by the tissue parasites, since chloroquine or some other quinine-successor drug, usually ineffective against tissue parasites, produces a cure when used to treat the primary attack. These cases probably represent a very light initial sporozoite inoculum which results in the development of an inadequate tissue stage.

Tissue stages of P. vivax malaria do not persist indefinitely. Even in fairly heavy initial infections, if chloroquine or other suppressant is given for about 18 months and then discontinued, ordinarily no relapses occur. Under such a regime the infection has "burned itself out" by releasing parasites periodically, which are destroyed by the suppressive drug before parasitemia is evident. There are cases, however, in which the tissue stage seems to last longer than two years. Probably these are due to a heavy initial sporozoite inoculum, or possibly to repeated infections.

In comparison, malaria due to P. falciparum (malignant malaria, estivoautumnal malaria) has only a short-lived tissue stage [5] (merozoites are released only once from the tissue parasites) and can be cured by a sufficient amount of chloroquine, quinine, quinacrine, or chlorguanide. Chloroquine is the drug of choice for the treatment of an acute attack. In insufficiently treated cases there may be a second attack as a result of recrudescence of parasitemia after cessation of treatment; however, this is not a true relapse, since it results from blood forms of the parasite which have not been eradicated by treatment.

In P. vivax malaria initiated by transfer of infected blood no tissue stages are formed. Although the recipient may become acutely ill with malaria, no relapses will occur after treatment sufficient to eradicate parasitemia, in contrast to the situation in a mosquito-induced infection.

In the Armed Forces during World War II P. vivax malaria caused excessive morbidity due to its tendency to relapse. This caused an intensive search for a drug which would eradicate the tissue parasites. For some years it has been known that pamaquine (Plasmochin) will eradicate the tissue stage of the P. vivax parasite, but this drug is too toxic for general use.

Recently primaquine,§ a related but considerably less toxic compound, was developed and tested against P. vivax malaria in human volunteers and was found to be effective against tissue parasites, with cure rates up to 100% in naturally occurring infections. Unfortunately, primaquine has little or no effect on the blood forms of the parasite; therefore, in treatment of acute attacks drugs active against blood parasites, such as quinine, chloroquine, quinacrine, or chlorguanide, must be given to eradicate parasitemia and terminate the fever. For permanent cure of the infection primaquine should also be given, as explained later.

Diagnosis of malaria should be made from thick blood smears. Methods may be found in any laboratory text or in the Wilcox "Manual."[15] Parasites cannot be found in a thin smear until considerable numbers are present in the blood, and use of a thin smear will only delay diagnosis.

During latency, diagnosis of P. vivax malaria cannot be made by any method. Blood smears will be negative repeatedly until relapse occurs.

TREATMENT

At present the recommended treatment of P. vivax malaria is chloroquine plus primaquine. Most of the first dose of chloroquine is absorbed by the tissues and is not available for eradication of blood parasites; consequently it is important to give a loading dose of 1.0 gm. of the diphosphate (0.6 gm. base), orally followed in six hours by 0.5 gm. (0.3 gm. base) and then 0.5 gm. on each of two succeeding days, making a total dose of 2.5 gm. (1.5 gm. base) in three days.

Primaquine is given in a single 15 mg. (base) dose daily for 14 days. Since primaquine is effective only against tissue parasites, it need not necessarily be given with chloroquine, though that method is preferable. In some cases nausea and vomiting may be too severe for primaquine to be given immediately and its administration can be delayed until the acute phase of the disease is controlled with chloroquine. In other cases primaquine may not be immediately available and chloroquine can be used to treat the acute attack and primaquine given later when it is obtained. If a delay of 40 or more days is anticipated before giving primaquine, the patient should be given suppressive doses of chloroquine diphosphate, 0.5 gm. (0.3 gm. base), once a week until a course of primaquine can be completed.

P. falciparum malaria should be treated with chloroquine alone, using the three-day schedule of dosage as given above. Chloroquine may be given by intramuscular injection (0.2 gm. base) when necessary,[16] completing the full course by the oral route.

No toxicity from primaquine is likely in either white[17] or Negro[18] patients at the dosage recommended. Some degree of methemoglobinemia may occur, but only rarely will this be of such severity as to merit discontinuing medication. Negro patients should be watched more closely for toxic signs. Hockwald and associates[18] have shown that intravascular hemolysis has occurred in some Negroes given 30 mg. of primaquine daily. This has not occurred in white patients, nor has it occurred in Negroes given 15 mg. daily. The only toxicity to be expected from chloroquine at the recommended dosage is an occasional case of urticaria or, rarely, slight nausea.

§ References 12, 13, and 14.

For a person living or traveling in a malarious area the recommended suppressive regimen is chloroquine diphosphate 0.5 gm. (0.3 gm. base) weekly. Immediately after leaving the area he should take primaquine 15 mg. (base) daily for 14 days. With a regimen of this type no attack of P. falciparum or delayed P. vivax is likely to occur.

Another new drug, pyrimethamine (Daraprim),[19] shows promise of being a good suppressant for P. vivax malaria. It is not recommended for treatment of acute attacks, because of its slow therapeutic action. It is an effective suppressant in minute doses, 25 mg. weekly being the recommended dose. There is some evidence that this drug may be effective against the tissue stages of the parasite, which results in suppressive cure of the disease.

SUMMARY

The primary aim of this paper has been to present a rationale of treatment of P. vivax malaria. To further that aim, discussion has been restricted to points pertinent to treatment, omitting mention of epidemiology and parasitology and clinical aspects of the disease. Discussion of malaria due to Plasmodium malariae (quartan) and P. ovale has been omitted entirely because these species are rarely seen in the United States. A limited discussion of P. falciparum malaria has been included, because such infections are seen on occasion.

Types of P. vivax malaria vary in relapse patterns according to geographic origin. Naturally acquired temperate zone strains show a long latent period corresponding to the winter months; tropical strains do not exhibit such latency.

Tissue stages of the P. vivax parasite, which are responsible for relapses, made permanent cure of the infection difficult until recently.

Tissue parasites may be eradicated by primaquine, 15 mg. (base) given as a single oral daily dose for 14 days, and the blood parasites by chloroquine, 2.5 gm. (1.5 gm. base) total dose orally over a three-day period.

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ASSOCIATION OF POLYURIA AND ALBUMINURIA WITH HYPERTENSION OF UNILATERAL RENAL ORIGIN

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EXPERIMENTAL renal hypertension in animals is associated with polyuria, albuminuria, and sometimes edema. These manifestations may be evident whether the hypertension results from manipulation of both kidneys or of one kidney. In the latter event the function of the normal kidney is apparently altered.

Since 1937, when Butler [4] reported the cure of a hypertensive child by nephrectomy, it has been known that unilateral kidney disease can cause reversible hypertension in humans. The review by Smith [29] in 1948 emphasized the difficulty of distinguishing these cases preoperatively. Perera and Haelig [24] have recently described one type of clinical history which, when present, can help in so distinguishing them. There have been many analyses of the underlying diseases of the affected kidney, but little emphasis has been placed on the effects of this type of process other than the elevation of arterial pressure, although such effects are well known in experimental animals.

A patient recently treated at Stanford University Hospital gave a striking history which suggested the possibility that there may be a change of renal function in humans characteristic of some cases of hypertension secondary to unilateral renal disease. This change is a modest decrease in concentrating ability, associated with polyuria, polydipsia, nocturia, and albuminuria. For this reason, although it is too soon after nephrectomy to establish the permanence of this patient's cure, her case will be presented. Some relevant experimental studies on animals and humans will be discussed. A few cases of hypertension demonstrated to have been of unilateral renal origin, selected from recent reports and from the bibliography of Perera,[24] will be mentioned, which reveal that these findings are not infrequent in such case reports even though they were not being specifically looked for.

REPORT OF A CASE

P. P., No. 288461, is a single woman of 28 doing clerical work. On April 6, 1953, she was refused by a blood bank as a donor because of hypertension.

Family History.—There is no family history of hypertension or of renal disease.

Previous Health and Illness.—She had no remarkable medical background. She had no previous knowledge of hypertension or history to suggest renal disease prior to the present illness. Results of urinalyses in 1945 and 1947 were reportedly normal. In August, 1952, when the patient was admitted to the hospital because of an acute gastrointestinal illness, the blood

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pressure was recorded as 124/74 and results of urinalysis were normal except for a "trace" of protein. In January, 1953, when she was again admitted for an acute febrile illness, her blood pressure was 120/80.

Present Illness.—In December, 1952, the patient became aware of mild intermittent ankle edema (tightness of the shoes and creasing of the skin). This would last a few days at a time and disappear for a few days. It was not related to menses or to any cardiorespiratory symptoms. It was associated with fluctuations of weight and with the onset of constipation.

In December and early January her friends commented to her that she was going to the bathroom often and that when she came out she would walk directly to the tap and drink about two glasses of water. This polyuria and polydipsia continued, and from February through April she found that she had started to get up once or twice during the night to void. She voided a very large amount each time without any symptoms of irritation or inflammation.

During March and April, she had four episodes of severe headache, abrupt in onset, starting when she was in bed, generalized and pounding in character, lasting 4 to 14 hours in spite of codeine and acetylsalicylic acid, phenacetin, and caffeine (Empirin), associated with nausea, trembling, and some perspiration. On April 21 she was admitted to the hospital for evaluation of the accidentally discovered hypertension. She had lost 12 lb. (5.4 kg.) in the previous three months.

Her blood pressures in the hospital averaged about 170/120 or 115. No diastolic reading below 110 was obtained. Other than the hypertension, results of her entire physical examination were normal, including examination of the ocular fundi, chest, heart, abdomen, flanks, and peripheral vessels. Blood count and sedimentation rate were normal. Urine had specific gravity of 1.004 and a "trace" of protein; it was otherwise normal. Blood urea was 20.6 mg., creatinine 1.1 mg., cholesterol 336 mg., and fasting sugar 107 mg. per 100 cc. Plasma protein was 7.0 gm. (albumin 5.0 gm.) per 100 cc. X-ray of the chest, including cardiac measurements, was normal. BMR was +8; electrocardiogram showed no abnormalities.

Phentolamine (Regitine) 5 mg. intravenously failed to lower the blood pressure.

Two 12-hour concentration tests were performed. On the first the maximum concentration was 1.008. On the second a concentration of 1.016 was attained. During each test the patient was strikingly uncomfortable from thirst.

Following the intravenous injection of sodium acetrizoate (Urokon), there was prompt roentgen visualization of a normal pelviocalicealureteral system on the right. At the end of 10 minutes there was a large amount of opacified urine in the bladder. A small amount of dye became visible in the left caliceal system only after 45 minutes and was still visible at two hours, although no dye remained visible on the right at this time. Retrograde pyelograms revealed normal anatomic configuration on both sides. The urine from both kidneys was sterile.

On May 3 the patient was discharged for observation at home.

On May 19 she was readmitted. In the interval she had experienced two violent prolonged headaches, the first of which had been accompanied by pain in the left flank. Fatigue and ankle edema had increased. Physical examination on her readmission revealed 2 diopters of papilledema bilaterally, with fine linear hemorrhages in both retinae but no exudates. Blood pressure was 180/110. Another, 11-hour, urine concentration test was done, the maximum specific gravity attained being 1.012, and again the patient suffered unusual thirst. Excretory urograms with sodium iodomethamate (Neo-Iopax) confirmed the previous findings, but a small amount of dye was seen on the left in 10 minutes, which led the radiologist to report, "There probably has been some increase in function of the left kidney, but this is still relatively poor. We still are postulating a vascular defect."

A left nephrectomy was performed on May 22, 1953, by Drs. King, Young, and Utzinger. No pulsation was felt in the renal artery. The operators' report read in part: "Approximately 1 cm. from the aorta there was a dilated fusiform portion of the left renal artery and this portion was about twice the size of the rest of the renal artery. This area was approximately 1 cm. in length and felt quite firm. The kidney was of normal color, small in size, and showed no infarcted areas. Following ligation of the renal vein the anaesthetist reported a drop in systolic blood pressure from 200 to 160."

At the close of the procedure the patient's blood pressure was 120/80. Her course after the operation was uneventful. Blood pressures were recorded daily. No systolic pressure was found higher than 130 and no diastolic higher than 85. Whereas preoperatively her fluid intake

(voluntarily selected) had ranged from 4.5 to 5.5 liters daily and her urine output from 4 to 4.5 liters daily, postoperatively she selected a 2.5 to 3.5 liter intake and her urine output varied from 1 to 2.5 liters. A concentration test on May 31 was carried for 19 hours without evident discomfort and her urine specific gravity rose to 1.024. Eight days after surgery the fundi showed no hemorrhages but papilledema was still present. One month after surgery, her fundi, blood pressure, urinalysis, and all her symptomatology had reverted to normal. Three months after surgery they were still normal.

Pathology.—Prior to receipt by the pathologist, the lumen of the main renal artery of the resected kidney had been injected three times with 2 cc. of sodium iodomethamate. X-ray examination of the injected specimen revealed uniform filling and normal ramification of the small vessels of the entire parenchyma. The specimen was then fixed whole in 10% formalin solution for several hours before dissection.

Examination of the partially fixed specimen showed it uniformly reduced in size. It weighed 75 gm. The capsule stripped cleanly, revealing a smooth surface. The cut surface showed normal markings, but the width of the cortex was reduced to about 3 mm. There was one cyst in the cortex, 4 mm. in diameter. The pyramids, calcyes, pelvis, and a 6 cm. segment of ureter were normal. The renal vein was normal. There were no accessory renal arteries. A 5 cm. segment of renal artery was ligated at its proximal extremity. The external diameter of the artery was uniformly about 3 mm., except in a segment 1 cm. long adjoining the point of ligation, where there was a fusiform enlargement to about 5 mm. in diameter. Eight cross sections of the artery at 5 mm. intervals showed no dilation of the lumen or distinct thickening of the wall.

Histological examination of the kidney showed marked atrophy of the subcapsular zone. The atrophic tubules were not separated by any significant amount of fibrous tissue, and there was no inflammation. The tubules in the deeper part of the cortex were not atrophied or dilated. The glomeruli were normal even in the atrophic zone. No conspicuous juxtaglomerular apparatus was seen. The arterioles were normal. The small and medium-sized arteries showed patchy mild intimal thickening. There was no pyelitis. Step sections of the main renal artery showed no intimal thickening in any segment. In the proximal 1 cm. of the artery the media was abnormally narrow and the adventitia was thickened. No medial scarring or degenerative changes were seen, and there was no inflammation of the media or adventitia.

It was concluded that this was an atrophic kidney due to a partial obstruction of the renal artery, which was not demonstrated in the portion of the artery removed.

REVIEW

This appears to have been a case of rapidly progressing "malignant" hypertension, resulting from partial occlusion of one renal artery. In both the recency of onset (normal blood pressure four months before nephrectomy) and the accelerated course to vascular and encephalopathic manifestations, as indicated by severe headaches and advanced changes in the fundi, it seems to conform to the criteria suggested by Perera and Haelig.[24]

Of particular interest were this patient's two additional complaints, of polyuria, nocturia, polydipsia and of ankle edema. Although both of these complaints were expressed to and recorded by each historian, they were understandably deemphasized after the demonstration of nearly normal urine, normal blood creatinine and proteins, and normal cardiac function.

The patient, however, believed that these symptoms were related to the present illness and dated its onset from their start rather than from the subsequently developing headaches and hypertension.

These changes in the metabolism of water and salt have been repeatedly produced in animals as by-products of the various procedures used in the investigation of renal hypertension since the original report of Goldblatt.[9]

Oster and Martinez,[22] while making rats hypertensive, either by wrapping one kidney in cellophane to produce perinephric scarring or by clamping one renal artery, reported that an increase of water consumption of about 76% occurred in hypertensive animals of both groups.

It might occur before, at the same time as, or after the rise in blood pressure. Once both were established, their fluctuations in degree tended to parallel each other. Urine volumes more than doubled and specific gravities fell. In this study albuminuria was not significantly increased. Green [11] found that the increased turnover of water and salt which followed renal encapsulation in rats regularly preceded by a number of weeks the development of hypertension. This closely parallels the course of events in the case presented, since the patient complained of polydipsia and polyuria in December but was still normotensive in January.

In the rabbit, Hughes-Jones, Pickering, and Prinzmetal [12] showed that the injection of renin or hypertensin produced an increased rate of urine flow as well as of chloride excretion and concluded, "the results suggest that the changes in the volume and composition of the urine during the diuresis produced by renin and hypertensin are due to suppression of the tubular capacity differentially to reabsorb water, sodium and chloride." This work is supported by that of Brandt and Gruhn [3] using renin in rabbits and by Sellers [26] using renin in rats, but its relevance to humans has been questioned by Smith.[28] Wright[32] discussing the action of renin and hypertensin in man, states, "the concentrating power of the kidneys is decreased." He refers to two of several careful studies that have been made on the effects of these agents on renal hemodynamics in both dogs and man.* Unfortunately, urine volumes are not mentioned in any of these reports.

Besides hypertension and a syndrome resembling diabetes insipidus, these methods have been shown to produce other effects in animals.

Both renin and angiotonin produce proteinuria.†

Renin may cause inhibition of body growth and loss of weight.[18]

Renal artery constriction in dogs may cause edema.[7]

If the mechanisms of renal hypertension are the same in humans as they appear to be in animals, it would be expected that some of the other sequelae which are seen in animals would be seen in the clinical cases as well. The patient reported here certainly manifested the polyuria and polydipsia. Her complaint of edema, her weight loss, and her minor proteinuria may also have been specifically related, but this is more difficult to feel sure about.

There are now many published cases of hypertension which has responded to nephrectomy and so has been accepted as renal in origin. It is not possible to tell by reviewing these reports what proportion of the patients may have shown similar changes. In many of the reports there is no mention of urine volumes, and no conclusions can be drawn from the specific gravity of one casual specimen.

In a few cases it has been specifically reported that there was no change in urine habits ‡; consequently, it can be accepted that such symptoms are not universally present at the time the patient is seen by the physician, but since these effects in animals are sometimes transient [1] even this fact would not necessarily imply that

* References 2, 5, 6, and 31.

† References 1 and 3.

‡ References 8 and 23.

there had not been a period of polyuria at the onset of the disease. Such a fact might not be elicited unless it were specifically sought after while the history was being taken.

For this reason no attempt has been made to survey all of the reported cases or to determine in what proportion such symptoms are mentioned, but a few cases of authenticated renal hypertension have been examined to see whether there were any which might suggest that these were common clinical findings. Those referred to below have been selected because they seem to be such cases.

Øster [21] gives a most convincing description. His case resulted from surgery, and the changes were under observation throughout their development and closely mimicked those seen in the experimental animal. "During the same period there has been pronounced pollakiuria and nocturnal enuresis." He reported the development of a 1+ albuminuria. He presented a graph of the preoperative and postoperative urine specific gravities and volumes, which showed a convincing change at the time of surgery. The average urine volume before surgery was 992 cc., specific gravity 1.012, and after surgery these figures were 693 cc. and 1.015. "The power of concentration and variability of the kidney had improved at once."

While none of the other cases was so completely reported, a number of them indicate similar changes.

Semans [27] describes a child in whom hypertension developed one month after abdominal surgery. It was apparently due to perirenal scarring. The hypertension was accompanied by albuminuria, increase in urinary frequency, and nocturia 5 to 6 times nightly.

Leadbetter [16] describes a case thus: "He had had enuresis or nocturia when aroused which became a more constant complaint before the last admission."

Kennedy and his co-workers § describe one thus, "Urinary frequency occasionally had been present. There was albumin in the urine."

Moore [20] describes a patient as having "nocturia three times a night for as long as she could remember." This patient had 2+ albuminuria.

Wallace [30] describes a patient, W. P., who, one year after a normal insurance examination, showed hypertension and nocturia. A concentration test raised the urine specific gravity only to 1.014.

Hyman [15] describes a patient thus: "He voided every four hours during the day and twice at night." There was a trace of albumin in this man's urine.

Goodman [10] describes a case due to unilateral renal artery occlusion, in which the history included two months of nocturia 4 to 5 times a night and polyuria. Again albumin was found in the urine, and the maximum specific gravity reached on a concentration test was 1.017.

In the case records of the Massachusetts General Hospital [17] there is one of a patient, known to be normotensive five months previously, who gave a story of three weeks of increasing nocturia 4 to 5 times a night.

Mathisen [19] reports the case of a child in which the most striking finding was an inhibition of growth.

§ References 13 and 14.

It would appear, then, that in a fair number of patients whose hypertension is of unilateral renal origin at least the polyuric and albuminuric and perhaps the other sequelae observed in the experimental animal may be observed if they are looked for. In those cases in which the polyuria is not found, it may be that a history of its previous presence can be elicited and that it might prove useful in dating the onset of the renal lesion.

COMMENT

The polyuria in these patients can not be attributed to the diseased kidney. In the patient presented, for example, urine formation on the involved side was so slow that the slight amount of sodium acetrizoate filtered could accumulate in the caliceal system and become roentgenologically visible 45 minutes after its injection, long after the much larger amount filtered on the good side had been diluted past visibility by the rapidly flowing urine. In some of the cases referred to, ureteral catheterization did not reveal significant amounts of urine coming from the diseased kidney. Neither are these functional alterations in the "normal" kidney the result of retention in the plasma of nitrogenous products, since plasma levels are routinely normal.

What the mechanism of this effect on the normal kidney by the diseased one is, is not clear. It is apparent that hypertensin can produce such effects. It has been suggested by Greene [11] that the mechanism may be related to that by which the adrenal steroids produce both hypertension and diabetes-insipidus-like states. Perhaps some of these patients may be useful in testing this hypothesis, since techniques of measuring and normal standards for steroid excretion by the human are now becoming available.

When the full symptom complex is present, as it was in the patient described here, it offers support to the belief that the hypertension is of renal origin. The involved kidney in this patient was not infected, and there was no surgical need to remove it other than that of controlling her malignant hypertension. Among the criteria for consideration of nephrectomy, presented by Schroeder and Fish,[25] are that the renal lesion should be confined to one kidney and that the combined renal function (urine concentration) must be within normal limits. The intent of these demands is still perfectly sound. It is possible, however, to have the normal kidney respond in such a manner that its function is demonstrably abnormal. A normal kidney under the influence of the renin-angiotonin mechanism excretes an abnormal amount of protein. The demonstration that there is some protein in the ureteral urine from the normal side then need not contraindicate surgery. A normal kidney under the influence of these agents may not demonstrate adequate concentrating power. In Wallace's patient, for example, the specific gravity reached only 1.014 on a concentration test, yet the success of surgery in his patient is attested by a normotensive follow-up which now extends over 10 years.

SUMMARY

A case is reported of a young woman in whom hypertension developed which was apparently relieved by removal of an atrophic kidney, distal to a diseased renal artery.

Her initial symptoms were not those of hypertension but those of polyuria and polydipsia. She also showed albuminuria, edema, and weight loss.

The literature on experimental renal hypertension is reviewed to comment on the relationship between the induction of these symptoms and the induction of hypertension.

A few case reports of hypertension cured by nephrectomy are reviewed to show that these renal effects are not uncommonly seen in human cases.

Dr. David A. Rytand gave many helpful suggestions during the review.

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SECONDARY NEOPLASMS OF THE HEART

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TRADITIONALLY, metastases to the heart have been considered to be a clinical curiosity or an incidental finding at the autopsy table. At the Laboratory of Experimental Oncology we have had the opportunity to follow to necropsy 288 patients with advanced neoplastic disease of wide variety. It has been our clinical impression that cardiac metastasis in patients with advanced neoplastic disease is of greater frequency and is more of a clinical problem than is generally recognized.

The frequency of secondary neoplasms of the heart, as reported in the literature, has been between 1 and 11% of patients with neoplastic diseases who have come to autopsy. Table 1 summarizes the frequencies as found in four large series. It is noteworthy that the reported frequency is considerably higher during recent years, probably reflecting increased interest in the problem. Another possible reason for the progressively higher frequency is that patients with advanced neoplastic disease are living somewhat longer, owing to various supportive medical measures, thus allowing more time for the development of such metastases.

Metastases to the heart have been found in all portions of the organ and its associated structures. According to Willis,[14] "evidence suggests that all parts are equally susceptible and different parts affected proportionately to their bulk." The secondary tumors may be single or multiple. They are most frequently found in the myocardium, but they may rarely be valvular or endocardial and protrude into the cavity of the heart.

All types of neoplasms have been implicated as the initial source of the metastases. The heart is usually one of several sites of metastatic spread; the lungs, the adrenals, the liver, and the lymph nodes are also involved in the majority of cases.* Rare cases have been reported in which myocardial metastases were the only ones found.† In most series, carcinomas of the bronchus and of the breast have been the chief offenders among the carcinomas, whereas melanoma and leukemia have been most frequently reported among the noncarcinomatous neoplastic diseases. Of 146 secondary tumors of the heart reported by Prichard,[13] 102 were from carcinoma, among which there were 23 carcinomas of the breast and 23 carcinomas of the lung; in the same series 26 sarcomas and 18 melanomas were found, giving these groups disproportionately large representations.

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* References 1 through 14.

† References 15 and 16.

The hematogenous route is the primary method of spread of metastases to the heart, with direct invasion and spread via tracheobronchial lymphatics making up only a small proportion of the reported cases. In the series of Raven [9] 72% of carcinomatous cardiac metastases were found to have spread by a hematogenous route as against 8% by direct extension and 5% by lymphatic channels, the remainder being due to a mixed hematogenous and lymphatic spread. In contrast, sarcomas were reported to have spread via the blood stream in only 37% of cases, with 50% having involved the heart by direct invasion from contiguous masses.

Most authors agree that most metastatic lesions of the heart are clinically silent. The diagnosis is infrequently made before death, probably because of the absence of characteristic abnormalities and relative lack of interest. Yater,[2] Scott, and Garvin,[4] Herbut and Maisel,[6] and Doane and Pressman,[7] however, have defined a clinical picture which, in the face of known neoplastic disease, would point attention to the possible presence of cardiac metastasis. This clinical picture, simply stated, consists of the rather sudden appearance of progressive and unresponsive signs and symptoms of almost any kind of heart disease in a person with a disseminated neoplasm and a previously normal heart. Most workers have stressed the infrequency with which these signs and symptoms occur, even in the face of extensive neoplastic infiltration of the heart.

TABLE 1.—*Frequency of Cardiac Metastases in Patients with Neoplastic Disease Coming to Autopsy*

Author	Date	Autopsies, No.	Cardiac Metastases, %
Symmers [1]	1917	298	1.6
Burke [3]	1934	327	4.3
Scott and Garvin [4]	1939	1,082	10.9
Dimmette [11]	1950	455	8.3
Present report	1953	288	18.0

Although the leukemias characteristically have diffuse parenchymal infiltration, frequently with alteration of function of the affected organs, little attention has been given to the subject of cardiac involvement and its possible complications. Wintrobe [17] stated that infiltrations in the myocardium are not infrequent and that pericardial effusions are not uncommonly found in patients with leukemia; cardiomegaly, abnormal murmurs, tachycardia, and cardiac failure may also be encountered. In 43 cases of leukemia of various types reported by Kirshbaum and Preuss [18] the heart was involved in 34%. The involvement consisted of a diffuse interstitial infiltration and/or plugging of small vessels of the heart by abnormal cells. Bierman, Perkins, and Ortega [20] reported from this laboratory four cases of pericarditis with effusion in patients with leukemia and suggested that "pericarditis with cellular infiltration occurs more frequently than is usually suspected in leukemic patients and may often contribute to their death." A study of eight patients with leukemia with abnormal electrocardiograms was made by Aronson and Leroy [21]; five of these patients had clinical manifestations of right or left heart failure. Dresdale, Spain, and Perez-Pina [19] have cited one case of complete heart block as a result of leukemic infiltration of the myocardium.

In view of the infrequency with which antemortem diagnosis of metastatic neoplasm to the heart has been made, it is not surprising that little attention has been

paid to possible therapy. Shelburne and Aronson [22] discussed a patient with carcinoma who in the course of illness developed pericardial effusion and complete heart block. It was presumed that these were due to metastases to the heart, and the patient was given a course of x-ray therapy to the heart with complete, though temporary, subsidence of the effusion and the abnormal electrocardiographic find-

TABLE 2.—*Primary Site and Type of Neoplasm and Frequency of Secondary Tumors of the Heart*

Autopsies		Cases with Cardiac Metastases,	
Diagnosis	No.	No.	% Frequency
Leukemia	(79)	(23)	(29)
Lymphatic	46	11	24
Monocytic	10	3	33
Myelogenous	20	6	33
Undetermined	3	3	—
Melanoma	21	10	48
Sarcoma	14	1	7
Glioma	3	–	–
Neuroblastoma	5	–	–
Lymphoma	17	2	12
Hodgkin's disease	26	–	–
Myeloma	7	–	–
Carcinoma	(116)	(17)	(15
Breast	5	–	–
Lung	24	5	20
Naso-oropharynx	21	3	14
Kidney	9	2	22
Testis	9	2	22
Colon	7	–	–
Ovary	6	–	–
Pancreas	5	–	–
Stomach	6	2	–
Prostate	1	1	–
Cervix and uterus	3	–	–
Esophagus	4	1	–
Thymus	4	–	–
Bladder	3	–	–
Liver	5	–	–
Adrenal	1	–	–
Undetermined	3	–	–
Total	288	53	18
Total of nonleukemic	209	30	14

ings. A similar case has been reported by Blotner and Sosman,[23] of a patient with chronic myelogenous leukemia, who developed a 2:1 heart block which cleared with local x-ray therapy on two occasions.

MATERIAL

During a consecutive period of 50 months, December, 1948, to February, 1953, there were 288 autopsy examinations on patients who died in the research ward of the Laboratory of Experimental Oncology. The population consisted of patients with a wide variety of neoplastic disease but was weighted heavily with leukemias and Hodgkin's disease (Table 2). Among these 288 patients were 53 (18%) with metastatic or infiltrative secondary neoplasms of the heart. These cases were reviewed according to pertinent pathological and clinical findings.

It should also be noted the patients admitted to this ward were selected for the extensiveness of their disease; therefore, many had widespread metastases when first seen and were moderately well adjusted to the presence of their neoplasms.

RESULTS

Primary Diagnosis.—Of the 53 patients found to have metastatic lesions of the heart, 23 had leukemia, 10 melanoma, and 17 carcinoma, giving frequencies for these groups of 29%, 50%, and 15%, respectively (Table 2). Notable by their absence from this group of 53 are patients with Hodgkin's disease and with carcinoma of the breast, both found in high frequency in other series.‡ With this exception, it is to be noted that there was a fairly uniform frequency of cardiac involvement of 15 to 20% in patients with disseminated neoplasms.

Mode of Spread.—In the large majority of cases the spread of the tumor was by the hematogenous route (approximately 90%). Most of the carcinomatous involvement consisted of discrete nodules in no proximity to the primary neoplasm and with no microscopic evidence of lymphatic involvement. In several cases lymphatic spread could be inferred from the presence of tumor strands in the lymphatic

TABLE 3.—*Type and Site of Cardiac Metastases in Fifty-Three Cases*

Type	% of Total	Leukemia	Sarcoma	Carcinoma	Melanoma
Nodular	37%	—	100%	86%	80%
50% left ventricle	....	..	.....	....	....
20% right ventricle	....	..	.....	....	....
25% auricle	....	..	.....	....	....
4% septal	....	..	.....	....	....
1% endocardium	....	..	.....	....	....
Diffuse	58%	100%	—	14%	—
Mixed	5%	—	—	—	20%

channel of the myocardium and of the pericardium. In only two cases was there clear-cut evidence of invasion directly from adjacent tumor masses (Table 3).

Site of Cardiac Involvement.—In view of the heavy weighting of this series with the leukemias (45%), the heart was found to be fairly diffusely infiltrated in the majority of cases (58%). Of the discrete nodular involvement 50% was in the left ventricle, 25% in the auricles, and 20% in the right ventricle. As would be anticipated, carcinomas generally produced discrete nodular or multinodular metastases (Table 3).

Other Metastatic Sites.—It is interesting that of the 30 nonleukemic patients with metastases to the heart, 26 also had pulmonary, 20 thyroid or adrenal, and 15 kidney metastases. In no case in this series was there cardiac metastasis without other visceral invasion. All patients with carcinoma that did not invade the heart directly also had pulmonary metastases.

Clinical Findings.—The most notable finding was the relative paucity of signs and symptoms of cardiac disease. One-half of the patients had no antemortem clinical evidence of cardiac involvement. In 27 patients, retrospective analysis revealed some findings that were attributable to cardiac metastases. In general, the clinical findings varied directly with the extent of involvement found at autopsy.

‡ References 4 and 6.

Two patients were definitely diagnosed before death as having cardiac metastases (see Cases 3 and 4). The difficulties of such definitive diagnosis are attested by the fact that during the same period in at least two other patients diagnosed clinically as probably having cardiac metastases the diagnosis was not substantiated at autopsy. The two patients with correct antemortem diagnosis of cardiac metastases had sudden severe arrhythmias associated with syncope, terminating promptly in death. Three other patients had clinical pericardial effusion. Four patients were noted to have an enlarged heart and were in congestive failure. Two of these patients had moderate pulmonary and peripheral edema, and digitalis was given, with equivocal results. Three of the four patients with congestive failure were elderly (65 to 72 years old), but in only one was there sufficient cardiac disease in addition

TABLE 4.—*Clinical and Electrocardiographic Findings in Fifty-Three Patients with Cardiac Metastases*

Finding	Patients, No.	Frequency, %
No antemortem cardiac disease noted	26	49
Clinical signs and symptoms *	27	51
Congestive failure	4	..
Pericardial effusion	3	..
Cardiomegaly	3	..
Arrhythmia	2	..
Tachycardia	2	..
Chest pain	2	..
Syncope	2	..
Murmur	1	..
Rub	1	..
Electrocardiographic abnormalities †	23	72
Left bundle branch block	2	..
AV conduction defect	1	..
Arrhythmias	2	..
ST-T changes	19	..
QRS changes	..	..
Low voltage	4	..
Abnormal Q waves	1	..
Notching or slurring	2	..
Elevated R in V_{1-3}	2	..
RSR pattern in all leads	1	..

* Including cases with electrocardiogram abnormalities only, and including listing of some cases under more than one finding.
† Electrocardiogram available in 32 cases only.

to metastases to explain failure on any other basis than the secondary neoplasm. Two patients complained of chest pain that was felt to be on a cardiac basis, and one had clinical and pathological evidence of coronary insufficiency (Table 4).

All patients with clinical signs and symptoms of cardiac disease also had abnormal electrocardiograms. Of the total 53 patients, cardiographic tracings were made in 32 and in 23 they were clearly abnormal. The majority of the records were read as "abnormal record of no characteristic pattern," and the abnormalities consisted chiefly of low-voltage, isoelectric, or slightly inverted T waves in the standard leads and over the left precordium (Table 4).

REPORT OF CASES

CASE 1.—A. L. M., a 72-year-old widow with a two-month history of increasing weakness, was referred with the diagnosis of myelogenous leukemia in October, 1951. The physical examination was not remarkable aside from pallor and a liver palpable 4 cm. below the right costal

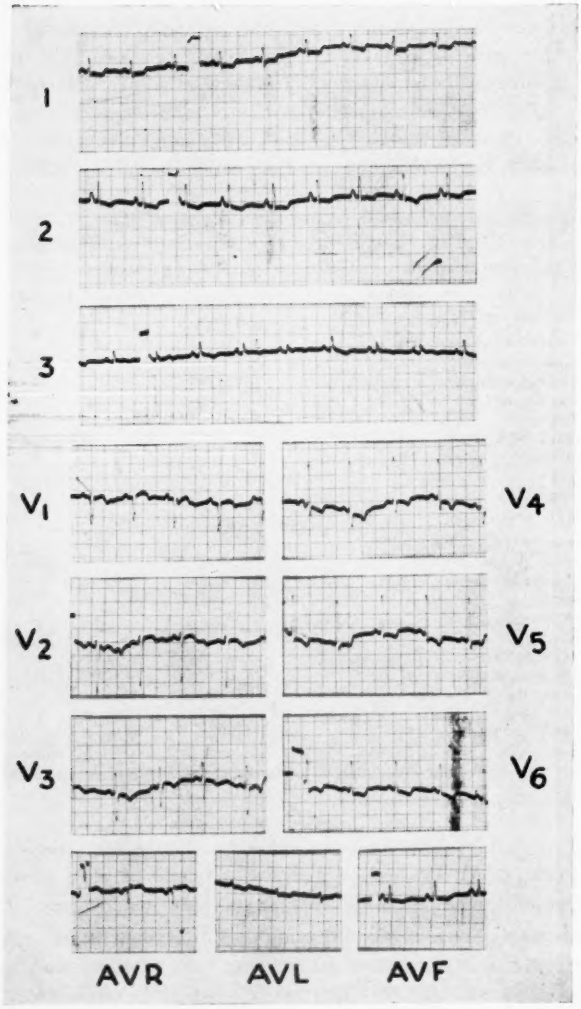

Fig. 1 (Case 1).—Electrocardiogram taken on the day of death, showing depressed ST intervals with inverted T in Leads I, II, III, V_3, V_4, V_5, V_6, aV_L, and aV_F.

margin. Her admission erythrocyte count was 2,100,000, and leucocytes 130,000, of which 67% were myeloblasts. During her 20-day hospital stay, the patient gradually went downhill. Two days before death shortness of breath and precordial pain developed and she was digitalized with ephemeral improvement. She died in November, 1951, in what appeared to be congestive failure, two days after digitalization.

An electrocardiogram taken on the day of death revealed depressed ST intervals, with inverted T in Leads I, II, III, V_3, V_4, V_5, V_6, aV_L, and aV_F (Fig. 1).

On autopsy examination of the heart there was seen generalized "blast cell" infiltration. There was no evidence of coronary artery disease. The lungs revealed marked myeloblastic infiltration, with generalized septal thickening.

CASE 2.—C. B., a 63-year-old ship fitter, in November, 1948, had a left nephrectomy for adenocarcinoma of the kidney. In December, 1948, a chest x-ray revealed a pulmonary mass and he received x-ray therapy directed to the chest and left kidney region. In March, 1949, he received treatment with nitrogen mustard, without improvement; in April, 1949, he became icteric and was believed to have infectious hepatitis, which cleared within the next two months.

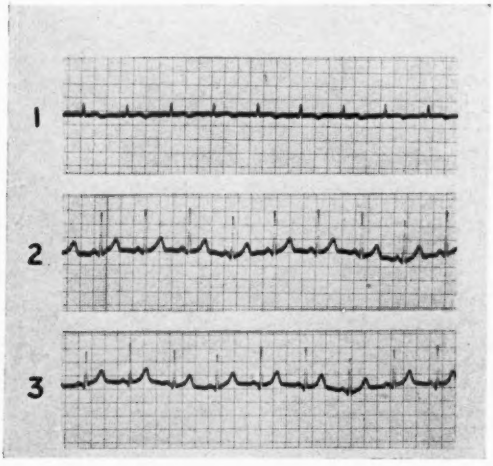

Fig. 2 (Case 2).—This electrocardiogram, taken 25 days before death, was essentially within normal limits in the standard leads.

In June, 1949, he was again given nitrogen mustard, this time intra-arterially. He became increasingly short of breath; a persistent tachycardia developed, and he died in July, 1949.

An electrocardiogram taken 25 days before death was essentially within normal limits in the standard leads (Fig. 2).

An electrocardiogram taken the day of death revealed a sinus tachycardia; QRS, 0.1, was broad, slurred, and notched in Leads I, II, V_5, and aV_L; isoelectric ST in Leads I, II, aV_L, aV_F, and V_6; slightly depressed T in Leads I and II (Fig. 3).

Autopsy examination showed the heart to be covered by a thick fibrinous exudate. There was a large tumor nodule in the interventricular septum and one nodule on the surface of the left ventricle. The coronary arteries had a moderate degree of atherosclerosis. The lung was massively infiltrated by neoplastic tissue.

CASE 3.—C. J. A., a 40-year-old clerk, had a widespread malignant melanoma, with the primary lesion on the right thigh, diagnosed in February, 1952. On entry, in October, 1952, he had subcutaneous, lymph node, hepatic, and pulmonary metastases. On the evening of his death, five days after entry, he suffered an attack of syncope while arising from bed. He was dyspneic and had a feeble irregular pulse of 60; within 30 minutes he died.

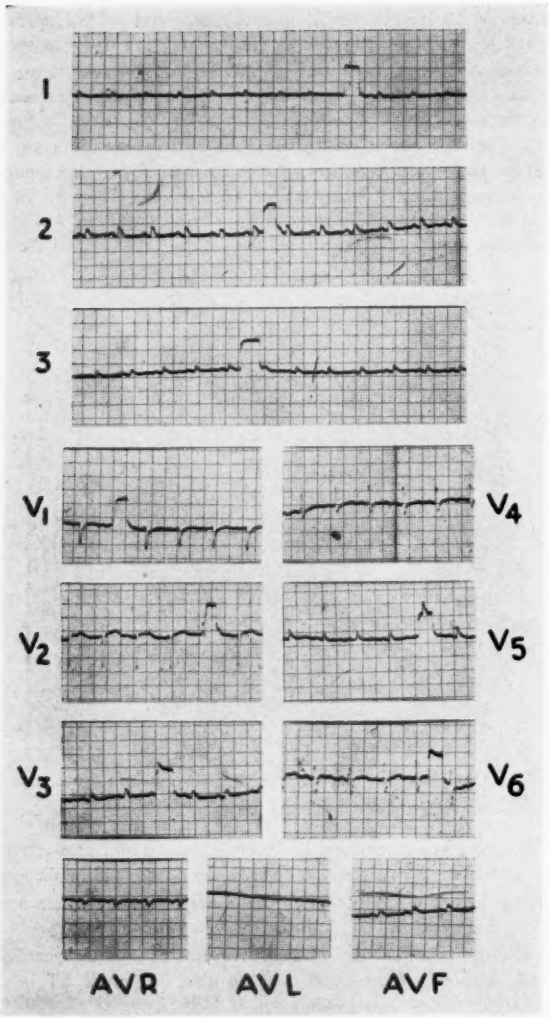

Fig. 3 (Case 2).—Electrocardiogram taken the day of death, revealing a sinus tachycardia. QRS, 0.1, was broad, slurred, and notched in Leads I, II, V_5 and aV_L; isoelectric ST in Leads I, II, aV_L, aV_F, and V_5; slightly depressed T in Leads I and II.

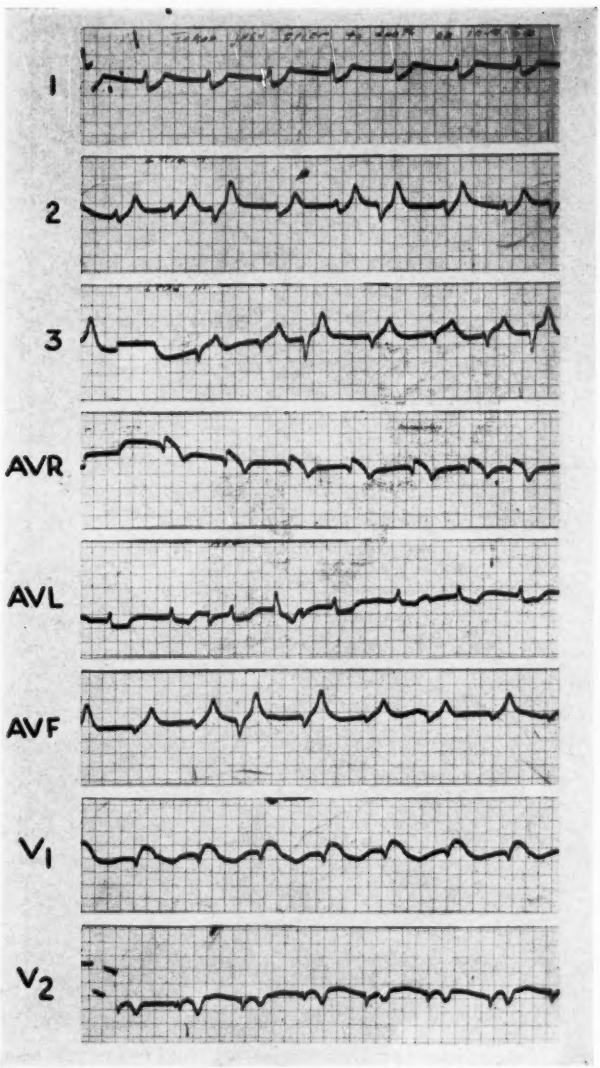

Fig. 4 (Case 3).—Electrocardiogram taken immediately prior to death, revealing a ventricular rate of 60, with a complete AV block. QRS, 0.12, bizarre complexes throughout probably representing left bundle branch block.

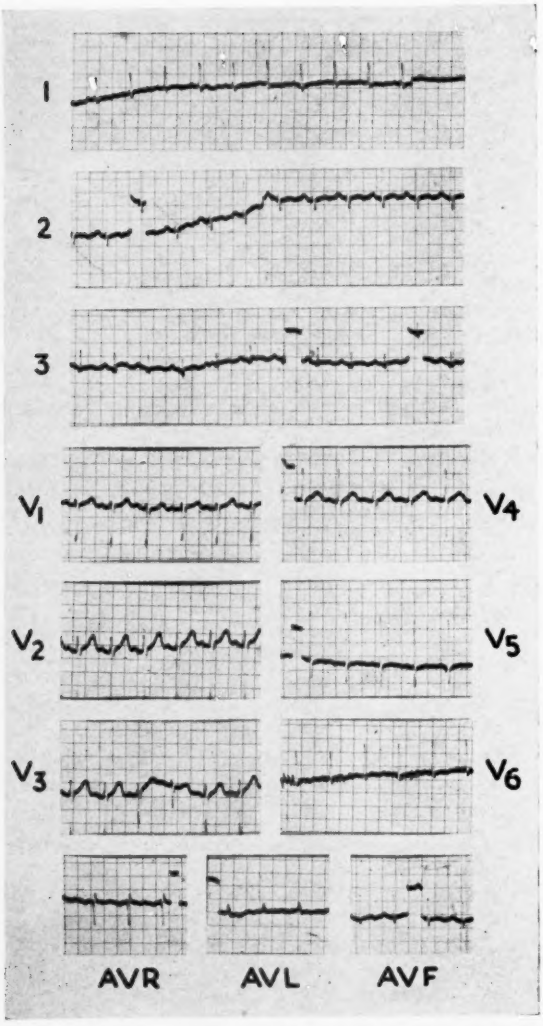

Fig. 5 (Case 4).—Electrocardiogram taken two months before death, revealing a sinus tachycardia, rate 120; isoelectric ST-T in Lead I; slightly elevated ST with diphasic T in Leads II, III, V_2, V_6, aV_F; slightly depressed ST and inverted T in Lead aV_L.

An electrocardiogram taken immediately prior to death revealed a ventricular rate of 60, with a complete AV block. QRS, 0.12 second, bizarre complexes throughout probably representing left bundle branch block (Fig. 4).

At autopsy tumor nodules were found throughout the heart. No septal lesions were reported. The lungs were massively involved by tumor, and metastases were present in other viscera.

CASE 4.—C. Y., a 50-year-old business man, had a widespread malignant melanoma, with the primary lesion arising from the sole of the left foot, which was diagnosed in August, 1951. On

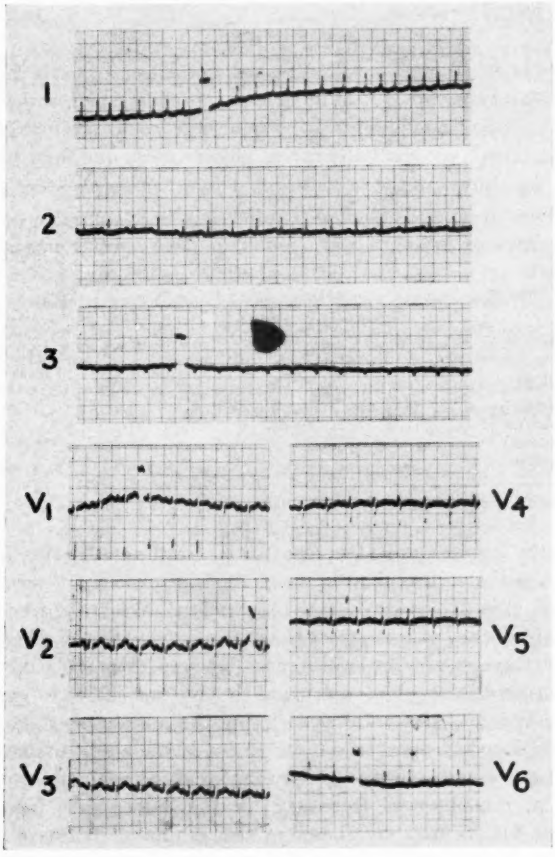

Fig. 6 (Case 4).—Electrocardiogram taken during syncopal attack 10 days before death, demonstrating a brief run of supraventricular tachycardia, rate 230, followed by sinus tachycardia, rate 145; low voltage QRS in Leads I, II, III, V_5, V_6, aV_L, and aV_F; notched Q-S in Lead III; tiny R with notch in Lead V_1; isoelectric ST-T in Leads I, II, III, V_5, V_6, aV_L, and aV_F.

entry, in September, 1951, he had massive edema of the left leg, and lymph node, subcutaneous, pulmonary, and hepatic metastases. He received several types of experimental drugs during his illness, without benefit. Ten days before death, in July, 1952, he had a sudden syncopal attack, associated with a generalized convulsive seizure; his pulse was slow and irregular. He regained consciousness gradually and thereafter went steadily downhill, without recurrence of similar episodes.

An electrocardiogram taken two months before death revealed a sinus tachycardia, rate 120; isoelectric ST-T in Lead I, slightly elevated ST with diphasic T in Leads II, III, V_5, V_6, and aV_F; slightly depressed ST and inverted T in Lead aV_L (Fig. 5).

An electrocardiogram taken during syncopal attack 10 days before death demonstrated a brief run of supraventricular tachycardia, rate 230, followed by sinus tachycardia, rate 145; low voltage QRS in Leads I, II, III, V_5, V_6, aV_L, and aV_F; notched Q-S in Lead III; tiny R with notch in Lead V_1, and isoelectric ST-T in Leads I, II, III, V_5, V_6, aV_L, and aV_F (Fig. 6).

At autopsy the heart was found to be studded with tumor nodules throughout the epicardium and myocardium, including the septa. The lungs were massively infiltrated with tumor, and there were many other visceral metastases.

COMMENT

Yater [2] in 1931 asked four questions regarding metastases to the heart: 1. Why are these metastases so rare? 2. Why is there predilection for the right heart? 3. Why are valves never involved? 4. Why is so little cardiac disturbance associated with large metastases? We shall attempt to answer these questions on the basis of this study and the studies in the literature that have appeared since Yater's article.

1. In the present series 14% of 209 patients with advanced neoplastic disease but excluding cases of leukemia were found to have cardiac metastases; this is

TABLE 5.—*Relative Frequency of Metastases to Four Organs as Related to Blood Flow to the Organ*

Organ	Blood Flow, Cc./Min.*	Frequency of Metastases, %
Heart	150	14
Thyroid	140	10
Adrenal	50	9
Kidney	550	8

* Data estimated from physiology and anatomy texts (References 27 and 28).

comparable to the frequency of 11% reported by Scott and Garvin. This frequency substantiates Willis' assertion that "the supposed infrequency of metastatic tumors in the myocardium is due to inadequate observation." When the frequency is compared with the frequency of metastases to other organs with a similar blood supply, it is found that there is very little difference between them. In patients with nonleukemic neoplastic diseases, 10% are found to have metastases to the thyroid, 9% to the adrenal, and 8% to the kidney.[14] Using the minute blood flow as a rough index of the likelihood of metastatic involvement of the above tissues, we find that the anticipated and the observed frequency for heart, adrenal, and thyroid are quite similar and that the observed frequency for the kidney falls below that to be expected (Table 5). We may say, therefore, that in tumors that have spread beyond the lung and liver filters there is almost an equal likelihood of the thyroid, the adrenal gland, and the heart to be involved with metastasis.

2. On the basis of bulk it would be anticipated that the left ventricle should receive the largest number of metastases. This is the case in the studies of Herbut and Maisel,[6] Willis,[14] and the present series. The impression of Yater, therefore, is not substantiated by the larger subsequent studies.

3. In view of the fact that metastases to the heart are usually the result of hematogenous neoplastic emboli there would be little likelihood that the relatively avascular valves would be involved. There was no such involvement in this series and very few instances in other series reviewed.

4. Most cardiac metastases are small and well localized and do not involve the full thickness of the myocardium. Unless they are located in or in proximity to the conduction tissue they would not be expected to interfere greatly with cardiac function. And, indeed, this minimal effect is evident in the present study and other reported series. The most that can be expected from such metastases is that they would alter the serial electrocardiogram. It is noteworthy that in the present series 23 of 32 patients had abnormal cardiograms. The question of patients with extensive lesions who demonstrated no signs or symptoms referable to cardiac involvement involves a consideration of heart reserve in a sedentary, often bedridden, person. Consideration must be given to the fact that a neoplastic infiltration of the heart probably allows sufficient time for the unaffected portions of the myocardium to adapt to the presence of the neoplasm. It is interesting that of the four patients in the present group who had congestive failure three were between the ages of 65 and 72, whereas the average age for the whole series was 38.

It has often been stated, in an effort to explain the supposed infrequency of metastases to muscle, that for some reason, probably related to the richness of the blood supply and the constant activity, neoplastic growth and muscle seem to be incompatible. Since metastases to the heart at least are not as infrequent as was previously presumed, we may now attempt to postulate regarding the compatibility of cardiac muscle and neoplasm. The heart has a rich blood supply, supplying a very actively metabolizing tissue; the blood supply is not adequate, however, to prevent oxygen extraction values of from 8 to 15 vol. %. In the coronary sinus the oxygen saturation varies from 12 to 53%, with an average of 23%, as compared with 70% for mixed venous blood.[24]

In general, the oxygen consumption of neoplastic tissue is found to be reduced when compared with the respiration of normal tissues.[25] The metabolism of the heart is notably aerobic, with a high coronary arteriovenous difference of lactic acid and little extraction of glucose. Glucose is removed by the heart in relatively small amounts, and lactic acid appears to be the keystone of myocardial metabolism. Tumors, on the other hand, are distinguished by a high anaerobic glycolysis. It has been observed that the venous blood leaving a tumor contains less glucose and more lactate than does venous blood draining a comparable normal site in the same animal.[26] We have, therefore, a parasitic tissue that demands less than normal quantities of oxygen and greater than normal quantities of glucose competing with a host tissue which has a very active aerobic metabolism and consumes greater than normal quantities of lactic acid. It would seem theoretically that these two tissues, therefore, are ideally suited to coexistence.

SUMMARY

Fifty-three cases of secondary involvement of the heart by neoplasm are reported from a total of 288 necropsies on patients with neoplastic disease. These cases are reviewed as to their frequency, distribution, and clinical and pathological characteristics.

It was found that 14% of patients with carcinoma and sarcoma and 26% of patients with leukemias had cardiac metastases or involvement.

Although a definite antemortem diagnosis of metastasis to the heart was made in only two patients, various signs and symptoms that in retrospect point attention to cardiac involvement were present in 50% of the cases. Variable but abnormal electrocardiograms were found in 23 of 32 patients.

The findings are compared with other series in the literature and their possible significance is discussed.

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NASAL INSTILLATION AND INHALATION OF CRYSTALLINE VITAMIN B_{12} IN PERNICIOUS ANEMIA

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AND
JOHN W. REBUCK, M.D., Ph.D.
DETROIT

SINCE the introduction of liver therapy by Minot and Murphy in 1926, the treatment of pernicious anemia has undergone many alterations simplifying procedures for both patient and physician. Oral administration of whole liver has been discarded because of the expense and the unpalatability of this material in sufficient quantity to be effective. Ingestion of liver extract, dessicated defatted hog stomach, liver-stomach concentrate, proteolyzed liver preparations, normal gastric juice, and vitamin B_{12} substances, as well as sublingual administration of vitamin B_{12} have not proved satisfactory for complete therapy of pernicious anemia. While folic acid corrects the hematologic disturbance, it does not favorably influence the neurological complications. The administration of massive doses of vitamin B_{12} by mouth produces adequate response in patients with Addisonian anemia,* but this mode of treatment is costly. Recent reports on the effectiveness of reaction products of vitamin B_{12} and intrinsic factor in oral therapy are encouraging although this preparation is expensive at the present time.[3] The success of parenteral injection of vitamin B_{12} is predicated upon the ready access of the injected material to capillaries of the blood and lymphatics. The material is carried in both the free and protein-bound state to the bone marrow to effect its hemopoietic activity.

One of the largest capillary beds in the body which contacts the external environment is that of the pulmonary circulation. Initially, inhalation therapy seemed to be a logical route for the administration of vitamin B_{12}. Reports of the effectiveness of aerosol therapy in other fields lends support to this concept.[4] Preliminary success in the administration of vitamin B_{12} by inhalation to patients with pernicious anemia has been encountered. Under ordinary circumstances, with the vehicles and equipment used in these investigations, only a small quantity of the inhaled material reaches the alveolar capillary bed. This indicates probable absorption of the vitamin B_{12} by the mucosal lining of the tracheobronchial tree. The similarity of mucosal structure in the nose suggested this organ as capable of absorption of vitamin B_{12} also. It was elected to administer this drug by nasal instillation.

From the Division of Hematology (Dr. Monto) and the Department of Laboratories (Dr. Rebuck), The Henry Ford Hospital.

* References 1 and 2.

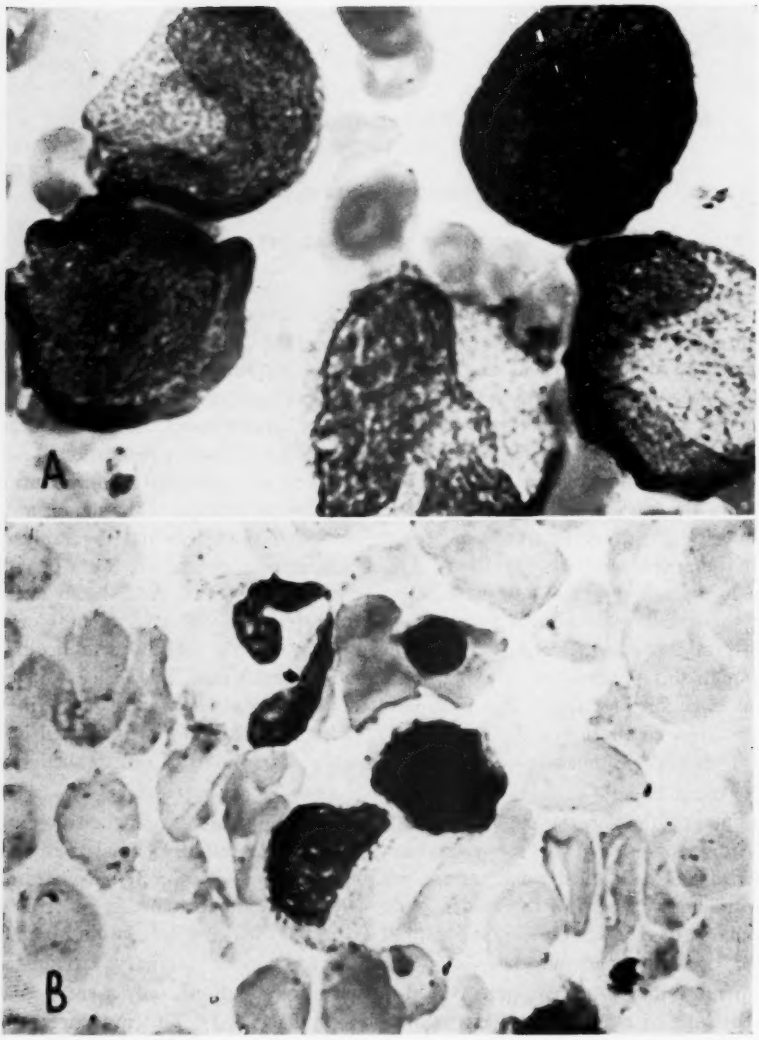

Fig 1.—*A*, representative megaloblasts and giant neutrophilic metamyelocytes in the marrow aspirate prior to treatment; × 1,200. *B*, normoblasts and unaffected members of the neutrophilic series in the marrow aspirate after nasal instillation of vitamin B_{12}; × 1,200.

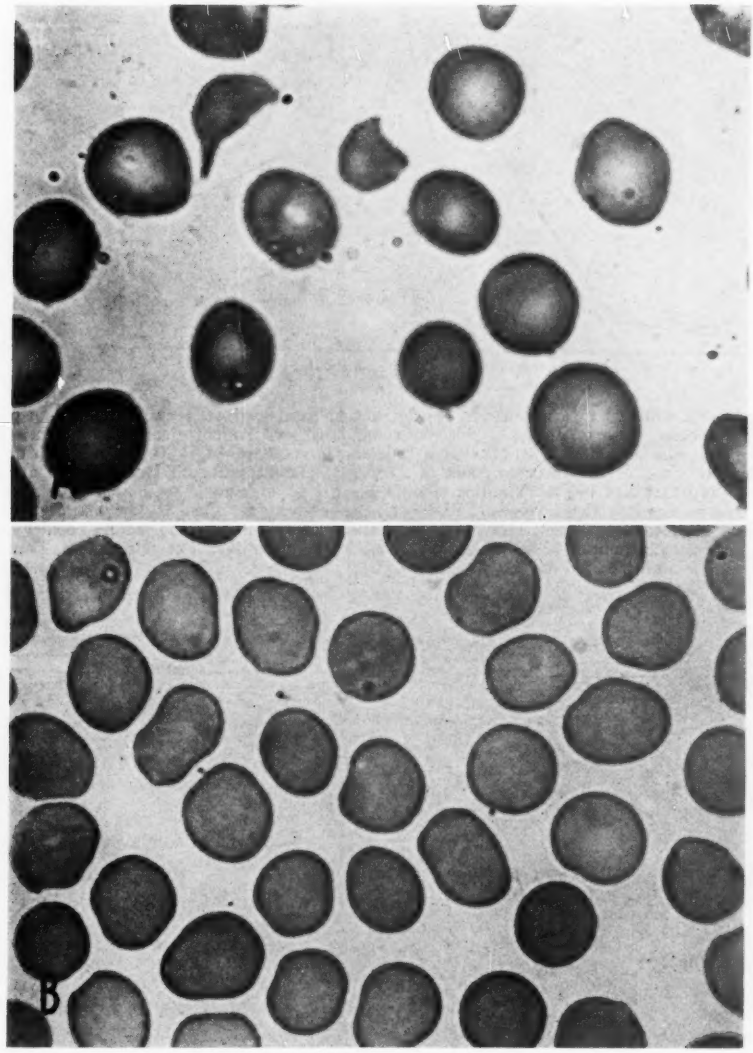

Fig. 2.—*A*, megalocytes and poikilocytes in the peripheral blood smear prior to treatment; × 1,200. *B*, normocytic peripheral blood smear after nasal instillation of crystalline vitamin B_{12}; × 1,200.

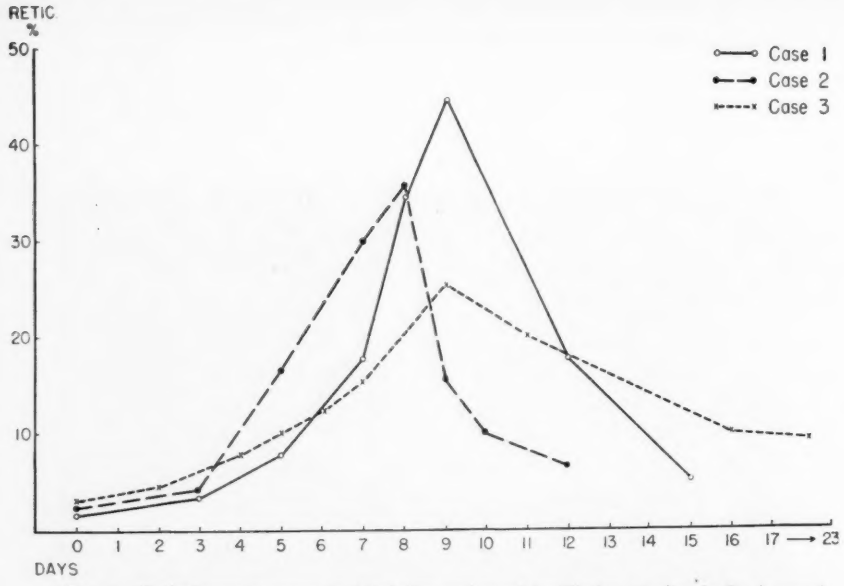

Fig. 3.—Reticulocyte response to inhalation and nasal instillation of vitamin B_{12} in pernicious anemia. Case 1: Initial erythrocyte count 1,360,000. Patient given daily inhalations of 15 γ vitamin B_{12} as aerosol. Maximum reticulocyte response, of 44.2%, on the 10th day of therapy. Case 2: Erythrocyte count of 2,880,000 before treatment. Patient given a single nasal instillation of 100 γ crystalline vitamin B_{12} in 1 cc. of isotonic sodium chloride solution, with a maximum reticulocytosis, of 35.8%, on the seventh day. Case 3: Original erythrocyte count of 1,640,000. Patient received 10 inhalations of vitamin B_{12} and lactose powder daily. A reticulocyte count of 22% was demonstrated on the ninth day. The reticulocytes remained over 10% until the 23rd day.

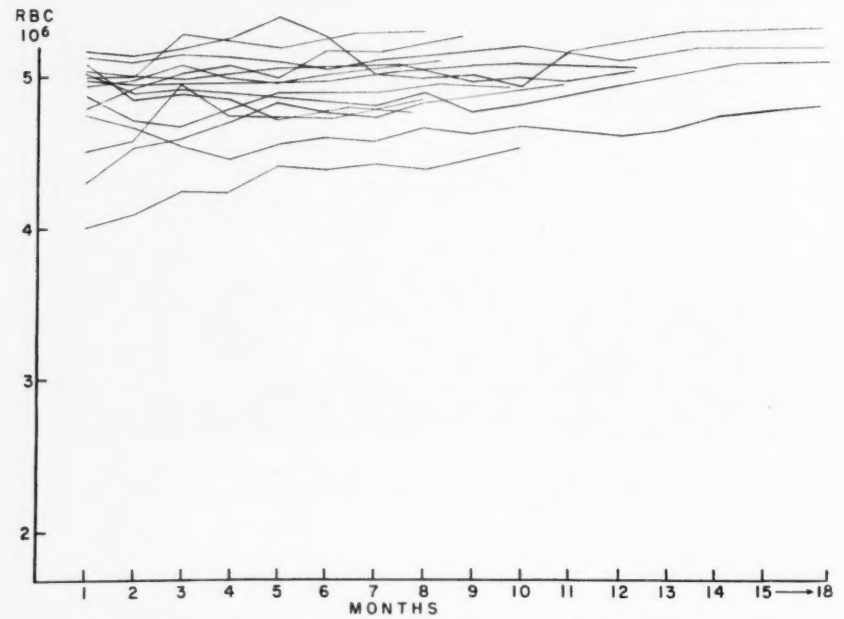

Fig. 4.—Maintenance therapy of pernicious anemia on vitamin B_{12} inhalation and instillation.

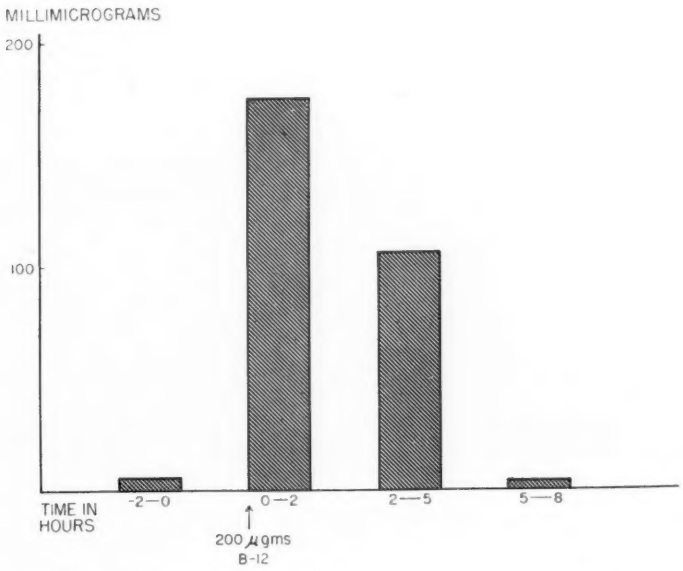

Fig. 5.—Urinary excretion of vitamin B_{12} after nasal instillation.

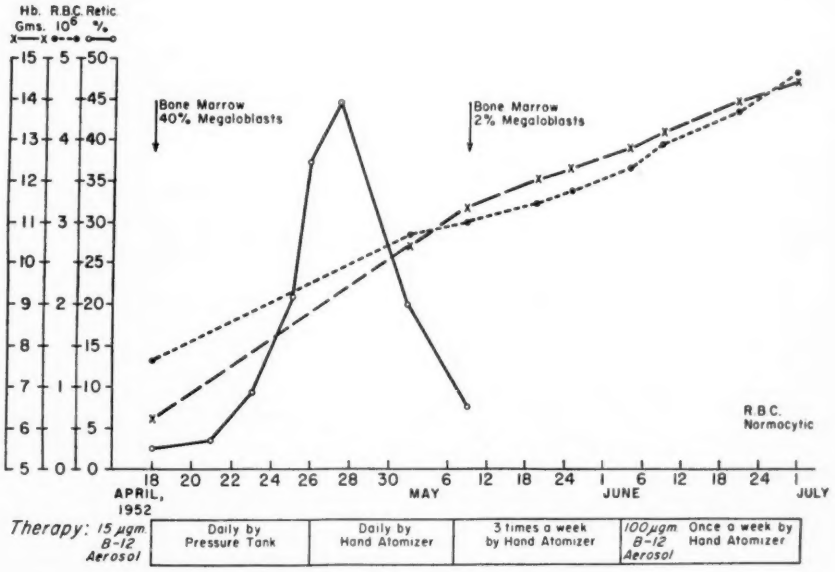

Fig. 6.—Vitamin B_{12} aerosol treatment of pernicious anemia in a 56-year-old man. This figure has been reproduced from an article by Monto and others [6] with the permission of the editor and publisher.

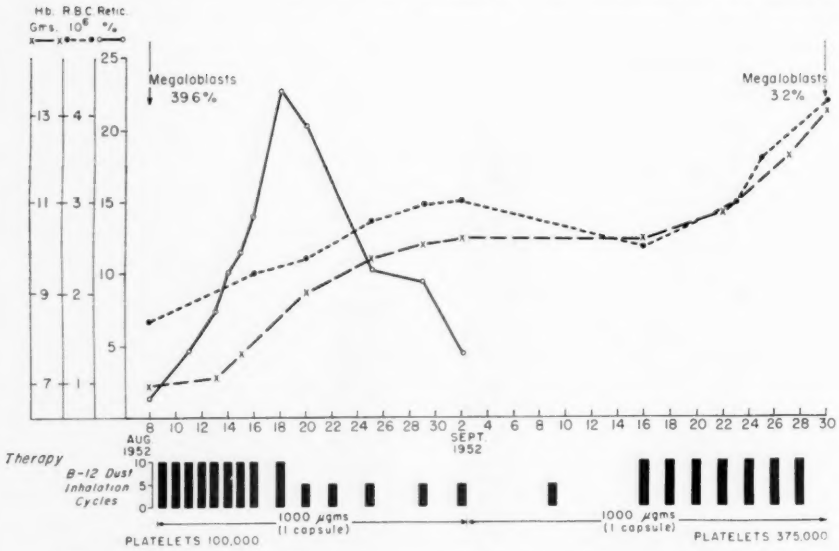

Fig. 7.—Vitamin B_{12} dust inhalation treatment of pernicious anemia in a 61-year-old man. This figure has been reproduced from an article by Monto and others [6] with the permission of the editor and publisher.

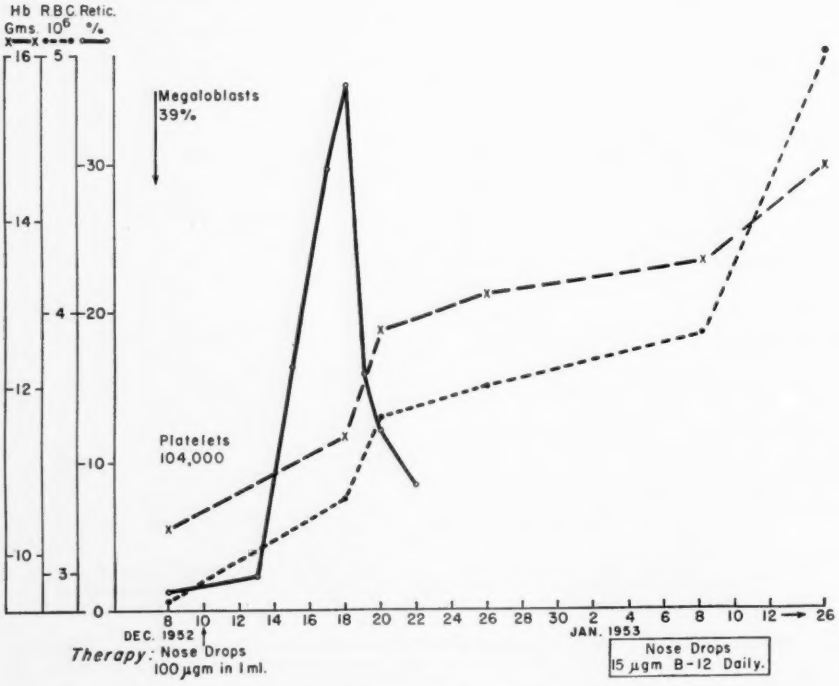

Fig. 8.—Vitamin B_{12} nasal instillation treatment of pernicious anemia in a 69-year-old man.

This report contains the results of treatment of 12 patients with pernicious anemia in relapse by both inhalation and nasal instillation of crystalline vitamin B_{12}. Twenty patients with pernicious anemia in remission were treated by these techniques for varying periods up to 18 months.

MATERIALS AND METHODS

The patients with pernicious anemia in relapse, in addition to the usual clinical syndrome including neurological manifestations, presented the classic hematological features of macrocytic anemia and megaloblastic arrest of the bone marrow. In each case achlorhydria was demon-

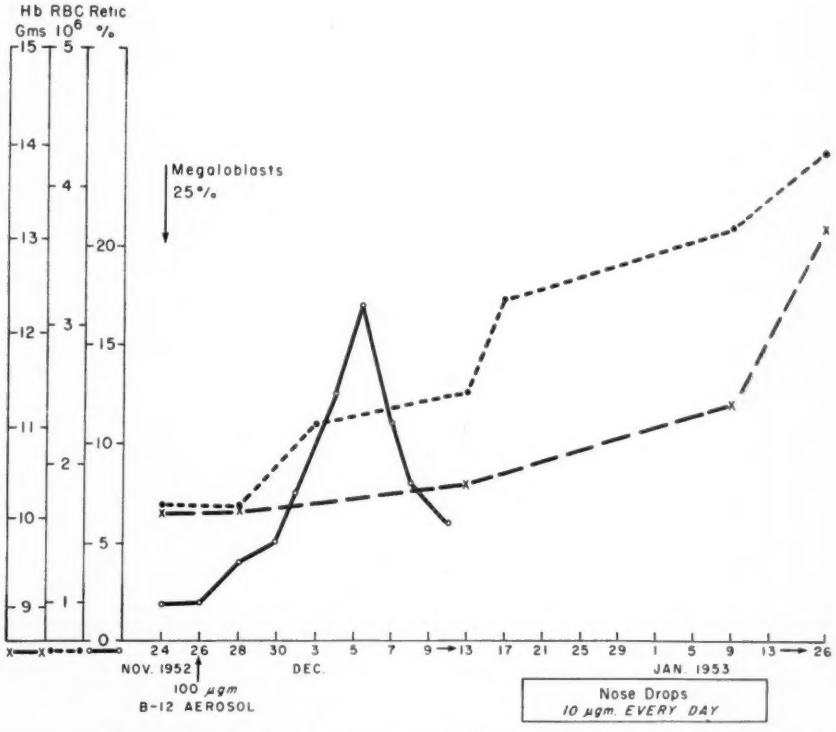

Fig. 9.—Vitamin B_{12} aerosol and nasal instillation treatment of pernicious anemia in a 82-year-old man.

strated after histamine injection. The condition of the patients in remission had previously been adequately controlled by the injection of either refined liver extract or vitamin B_{12} at intervals of two to four weeks.

Crystalline vitamin B_{12} in isotonic sodium chloride solution without a preservative was utilized for aerosol inhalation and nasal instillation. Maximum hemopoietic effect was elicited with a solution containing 100 γ per ml., although in these observations the concentrations employed varied from 15 γ to 200 γ per milliliter. One thousand micrograms of vitamin B_{12} in 1/10 ml. by volume of lactose powder was used for administration as a dust. Experience with inhalation technique demonstrated greater effectiveness if a forced expiration immediately preceded a slow, deep inspiration after which the breath was held for a few moments and then exhaled through the nose. Nasal instillation was performed in 0.5 ml. volume divided between the two nostrils and given in the usual manner of nasal liquid medicaments.

RESULTS

In each of the 12 patients with pernicious anemia in relapse treated by inhalation and nasal instillation a satisfactory hematological and clinical response was obtained. Maximum reticulocyte increase occurred between the 8th and 10th days of treatment and varied between 18 and 44%, correlating with the severity of the anemia. Erythrocyte production ranged from 300,000 to 500,000 per cubic millimeter increase a week. The bone marrow picture reverted from a megaloblastic arrest to normal erythropoiesis, and the peripheral blood findings reflected this

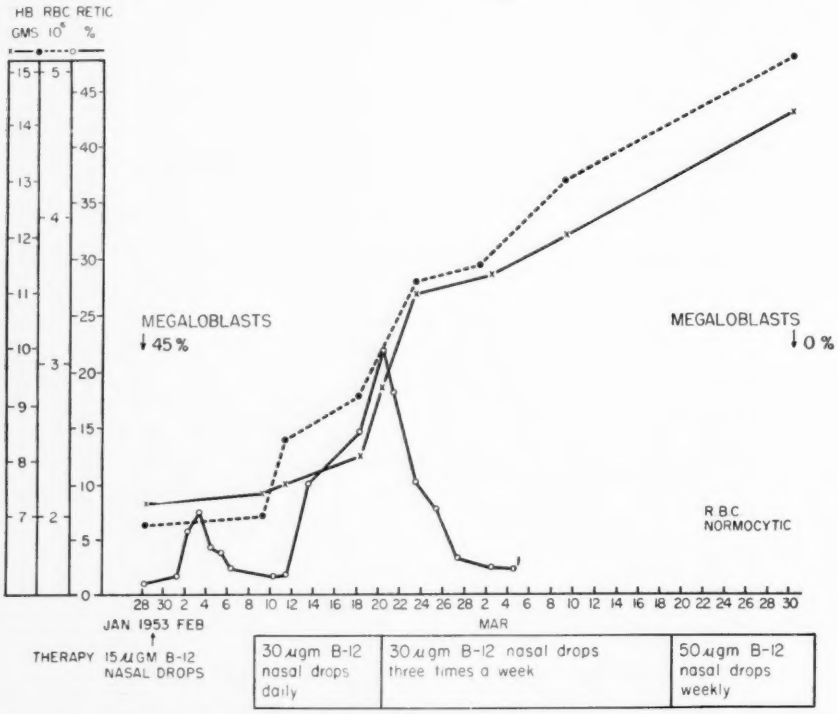

Fig. 10.—Vitamin B_{12} nasal instillation treatment of pernicious anemia in a 63-year-old man.

improvement (Figs. 1 and 2). Regression of the mucous membrane changes and neurologic manifestations occurred in the same degree as observed in patients treated with parenteral vitamin B_{12}. A single inhalation of 100 γ of crystalline vitamin B_{12} in 1 ml. of isotonic sodium chloride solution produced a reticulocyte elevation to 18% in a patient whose initial erythrocyte count was 1,020,000. Instillation of 100 γ in 1 ml. of saline solution effected a reticulocytosis of 37% in another patient with pernicious anemia, whose original red cell count was 2,880,000 (Fig. 3). In another patient, with an erythrocyte count of 1,940,000, a single nasal instillation of but 15 γ produced submaximal reticulocyte increase to 8%. Figure 4 illustrates the ability

of inhalation and nasal instillation of vitamin B_{12} to maintain, for varying periods up to 18 months at this writing, a favorable condition in patients with pernicious anemia in relapse.

COMMENT

The suitability of vitamin B_{12} inhalation and nasal instillation therapy requires some amplification. Few drugs now being used by this route of administration meet

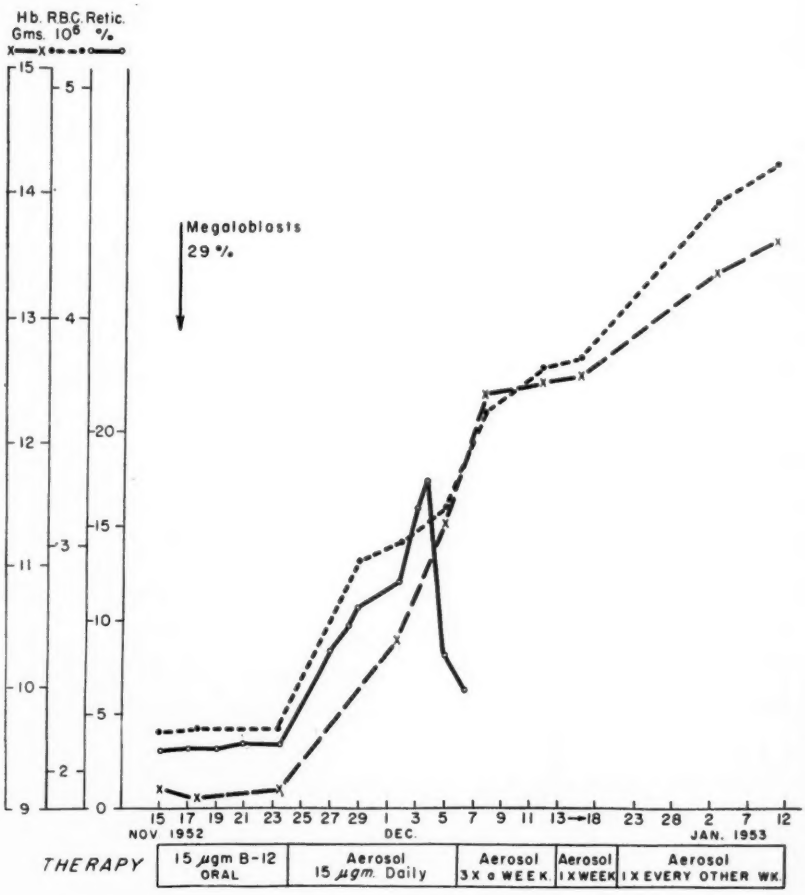

Fig. 11.—Vitamin B_{12} aerosol treatment of pernicious anemia in a 66-year-old man.

the exacting requirements of lack of toxicity and need for closely controlled dosage. Inhalation and nasal instillation of crystalline vitamin B_{12} in isotonic sodium chloride solution or lactose powder has, to date, produced no objective or subjective evidence of toxicity or sensitivity at the local site.

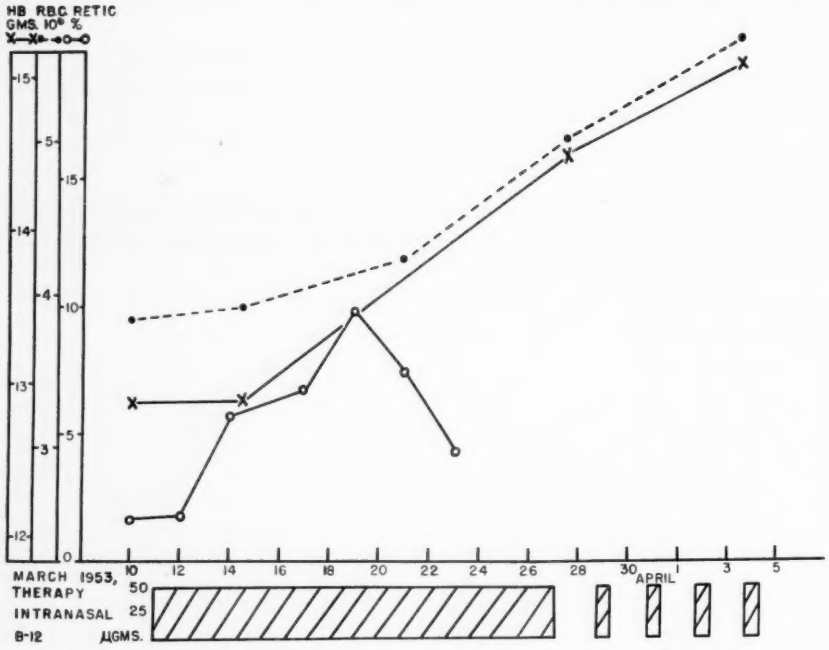

Fig. 12.—Intranasal treatment of pernicious anemia with vitamin B_{12} in a 63-year-old man.

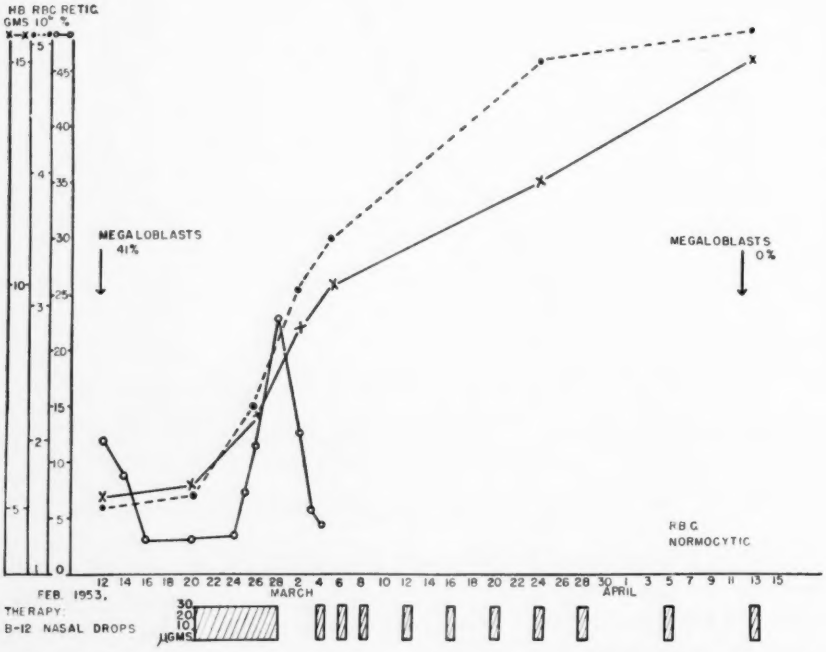

Fig. 13.—Vitamin B_{12} nasal instillation treatment of pernicious anemia in a 36-year-old man.

After parenteral injection of 15 γ of vitamin B_{12} or oral administration of amounts as high as 10,000 γ, urinary excretion is less than 0.05 m γ per cc. of vitamin-B_{12}-like growth substance as measured by the test organism Lactobacillus leichmanii.[5] After 200 γ of vitamin B_{12} in solution was inhaled, vitamin B_{12} activity in the urine reached the level of 0.26 m γ per cc., and after the inhalation of 500 γ of vitamin B_{12} in lactose powder vitamin B_{12} activity in the urine rose to 0.134 m γ per cubic centimeter. Direct pulmonary instillation of 100 γ of vitamin B_{12}, by means of a bronchoscope, resulted in urinary excretion of 9.76 m γ per cubic centimeter. Nasal instillation of vitamin B_{12}, similarly, resulted in significant amounts of vitamin B_{12} activity in the urine (Fig. 5). These data suggest that "intrinsic"

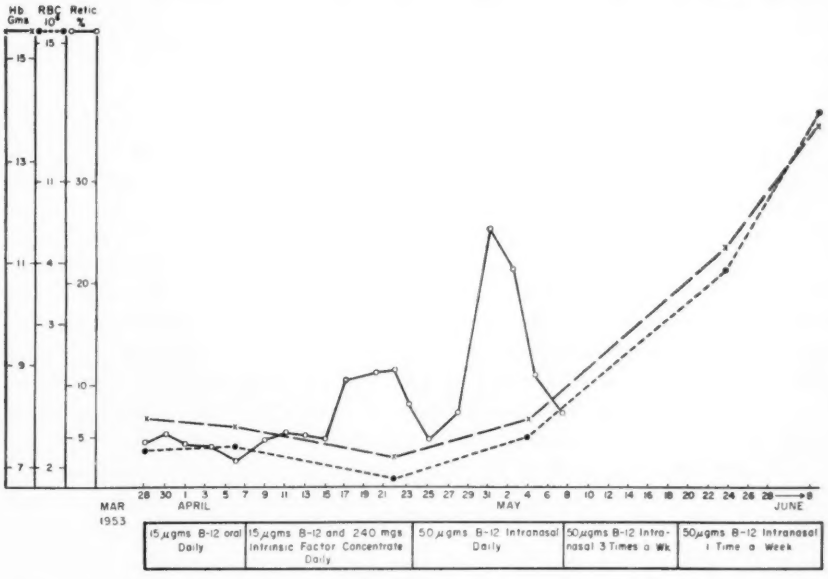

Fig. 14.—Vitamin B_{12} oral and intranasal treatment of pernicious anemia in a 67-year-old woman.

substance is not essential for the absorption of vitamin B_{12} from the mucosa of the respiratory tract.

SUMMARY AND CONCLUSIONS

Inhalation and nasal instillation of crystalline vitamin B_{12} in isotonic sodium chloride solution and lactose powder has resulted in adequate clinical and hematological response in 12 patients with pernicious anemia in relapse. The condition of 20 patients with pernicious anemia in remission has been maintained for periods up to 18 months. Detectable amounts of vitamin-B_{12}-like growth substance in the urine were found after pulmonary administration and nasal instillation of this substance. This simple form of therapy is not only effective, but safe and economical.

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FIBRINOGEN CONCENTRATION IN ACUTE MYOCARDIAL INFARCTION

Comparison of the Clot Density Determination of Fibrinogen with the Erythrocyte Sedimentation Rate

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BROOKLYN

THE ERYTHROCYTE sedimentation rate (ESR) is commonly employed for the clinical evaluation of acute myocardial infarction.* Ever since the ESR was introduced into medical practice by Fahraeus, in 1921,[13] it has been known that the fibrinogen concentration of the plasma is of foremost significance in the production of rapid settling of the red blood cells. Frequently, however, secondary factors influence the suspension stability of the blood, such as the various globulins,† cholesterol,[17] the viscosity of the plasma,‡ the size of the red blood cells,‡ the volume of packed red cells,§ and the electrostatic charge of the proteins and the red blood cells.[16] It is obvious, therefore, that a method which depends on a great number of factors is bound to produce bizarre results even under the most carefully controlled conditions and even when a standardized technique is used.

Thus, a method would offer a distinct clinical advantage if it were to determine only the predominant factor involved in the ESR—namely, the fibrinogen concentration of the plasma. Moreover, the practical application would be enhanced if such a procedure could be carried out without technical difficulties. These criteria seem to have been met by the clot density determination of fibrinogen as elaborated previously by two of us (S. L. and B. W. V.).[22]

This method is based upon the photoelectric determination of prothrombin time.[23] The fibrinogen concentration is derived from the difference of the optical densities of the plasma before and after clotting as read from the upper (optical density) scale of the Coleman Spectrophotometer Junior Model 6A. This determination can be performed within a few minutes, utilizing only 0.1 ml. of plasma. Furthermore, it furnishes two results independently in one procedure, namely the prothrombin time as well as the fibrinogen concentration.

From the Division of Laboratories, Jewish Sanitarium and Hospital for Chronic Diseases, and Kings County Division, Department of Medicine, Kings County Hospital.

* References 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

† References 14, 15, and 16.

‡ References 13 and 14.

§ References 18, 19, 20, and 21.

METHODS

Clot Density Determination of Fibrinogen.—Venous blood was withdrawn and added in a ratio of 9:1 to 0.1 M. solution of sodium citrate. After centrifugation, 0.1 ml. of plasma and 0.1 ml. of fresh rabbit brain thromboplastin (Difco) were placed in a cuvette measuring 6 mm. in diameter and 7.5 cm. in length.‖ The mixture was then incubated in a water bath at 37 C. for three minutes. Thereafter, the cuvette was placed into the microadapter of a Coleman Junior Spectrophotometer Model 6A with the wavelength set at 500 mμ and 0.1 ml. of 0.02 M. solution of calcium chloride was blown swiftly into the cuvette. At this point, the optical density was read from the upper (optical density) scale and recorded. At the instant of clotting the galvanometer light beam suddenly began to move to the left. The final optical density was read and recorded, and the first value was subtracted from the second reading. The difference, multiplied by 100, was termed "clot density." From this value the fibrinogen level was calculated according to the following, previously elaborated, formula [22]:

$$F = 18d + 120$$

where F indicates fibrinogen in milligrams per 100 ml. of plasma and d represents the clot density. The clot density in normal persons of either sex ranges from 5 to 15, corresponding to a fibrinogen concentration ranging from 210 to 390 mg. per 100 cc.

Sedimentation Rate.—The corrected sedimentation rate was determined according to Wintrobe's method.[21]

MATERIAL

A. Fifty cases proved clinically to be acute myocardial infarction were studied serially. Ten cubic centimeters of venous blood was withdrawn every other day and distributed into two tubes. The first tube contained 0.5 cc. of 0.1 M. concentration of sodium citrate and was filled up to the 5 cc. mark. It served for the determination of the fibrinogen concentration by the clot density method. The second tube contained balanced oxalates for the determination of the corrected sedimentation rate according to Wintrobe.

A white blood cell count was made simultaneously. While earlier in this study the determination of the white blood cell count was performed sporadically, it was subsequently instituted as a routine procedure whenever the ESR and fibrinogen concentration were determined.

In each instance the diagnosis of acute myocardial infarction was substantiated by serial electrocardiographic changes.

B. Six patients with myocardial infarction complicated by recurrent left ventricular failure were followed serially, comparing the ESR with the fibrinogen concentration.

C. Six patients with chest pain of varying severity diagnosed as coronary insufficiency because electrocardiographic studies had failed to reveal serial changes compatible with myocardial infarction were studied similarly.

The patients included in the present study were observed during the acute illness, which ranged from four to six weeks, and so their subsequent clinical course was not evaluated.

RESULTS

A. As seen in the Table, those patients who showed a high fibrinogen concentration as derived from the clot density values did not necessarily display a correspondingly high ESR. Thus, in Cases 1, 2, and 3, in which there were exceedingly high concentrations of fibrinogen during the first week of illness, namely, 1,308, 1,020, and 1,002 mg. per 100 cc., respectively, there were corresponding maximum ESR values of 23, 27, and 14 only. With declining maximum fibrinogen concentrations during the first week the corresponding maximum ESR tended to increase. It can be noted that the mortality among the 19 patients having a clot density above 38, corresponding to a fibrinogen concentration exceeding 804 mg. per 100 cc., is considerably higher than in the group of the remaining 31 patients. While the over-

‖ Manufactured by Standard Scientific Supply Corp., New York 12.

Data for Fifty Patients with Acute Myocardial Infarction

Patient	Age	Sex	ECG	Maximum Values During 1st Wk. of Illness				Remarks
				ESR (Corr.)	Fibrinogen Concentration * in Terms of Clot Density	Hematocrit Level	WBC	
L. W.	39	M	Ant. wall infarct	23	66	53	22,000	.....
H. W.	65	M	Post. wall infarct	27	50	52	17,200	Died
H. A.	79	M	Post. wall infarct	14	49	61	19,000	Died
D. S.	71	M	Ant. wall infarct	47	49	40	11,600	.....
E. W.	54	F	Post. wall infarct	50	49	42	12,000	Died
H. W.	45	M	Ant. wall infarct	36	48	51	14,700	.....
R. C.	71	F	Post. wall infarct	54	45	41	13,500	.....
A. N.	42	M	Ant. wall infarct	25	45	51	15,000	.....
A. G.	51	M	Ant. wall infarct	27	43	54	13,050	Died
B. P.	38	F	Ant. wall infarct	50	43	45	14,000	.....
S. G.	72	M	Ant. wall infarct	46	42	47	19,300	Died
L. M.	51	F	Post. wall infarct	40	40	45	12,000	.....
F. H.	46	M	Ant. wall infarct	38	40	45	14,550	.....
N. D.	61	M	Ant. wall infarct	36	40	44	10,100	Died
K. A.	65	M	Ant. wall infarct	41	40	43	10,000	.....
R. B.	67	M	Ant. wall infarct	41	40	47	7,000	.....
S. G.	64	F	Post. wall infarct	43	39	45	11,500	Died
M. B.	66	F	Ant. wall infarct	41	39	43	12,550	Died
S. F.	80	F	Post. wall infarct	45	39	44	19,200	.....
J. G.	58	M	Ant. wall infarct	36	36	42	6,600	.....
H. S.	41	M	Ant. wall infarct	37	36	45	12,200	.....
N. R.	76	F	Post. wall infarct	47	36	38	7,600	.....
L. D.	81	F	Ant. wall infarct	48	36	39	14,300	.....
M. Y.	63	F	Ant. wall infarct	50	35	45	7,500	.....
M. K.	67	F	Ant. wall infarct	50	35	42	9,600	.....
P. P.	74	M	Ant. wall infarct	30	34	46	14,800	Died
M. P.	42	M	Ant. wall infarct	39	34	45	7,800	.....
A. J.	59	M	Ant. wall infarct	37	34	44	12,000	.....
H. S.	39	M	Ant. wall infarct	40	33	47	17,400	.....
N. L.	55	M	Post. wall infarct	40	32	46	7,700	.....
M. V.	73	F	Post. wall infarct	47	31	45	13,600	Died
R. H.	68	F	Post. wall infarct	49	31	45	13,600	.....
M. B.	74	F	Ant. wall infarct	30	31	45	12,800	.....
M. H.	72	M	Ant. wall infarct	24	30	52	11,200	.....
H. L.	40	M	Post. wall infarct	43	30	45	14,200	.....
N. S.	65	M	Post. wall infarct	37	30	44	9,600	.....
M. S.	61	M	Post. wall infarct	41	29	47	13,600	.....
R. S.	72	F	Post. wall infarct	48	29	42	10,500	.....
H. L.	65	M	Post. wall infarct	16	29	52	16,300	.....
L. S.	62	F	Ant. wall infarct	43	28	44	12,100	.....
B. N.	65	M	Ant. wall infarct	36	28	43	11,500	.....
A. R.	72	M	Post. wall infarct	38	26	44	9,400	.....
B. L.	74	M	Ant. wall infarct	39	25	46	8,550	.....
B. A.	52	M	Ant. wall infarct	35	25	45	10,500	.....
A. E.	68	F	Post. wall infarct	35	24	43	14,500	Died
I. A.	70	M	Post. wall infarct	39	25	45	10,800	.....
W. G.	40	M	Post. wall infarct	31	24	46	13,200	.....
S. F.	64	M	Ant. wall infarct	41	24	46	16,000	.....
J. K.	62	M	Ant. wall infarct	39	23	45	18,650	.....
G. N.	50	M	Ant. wall infarct	40	22	47	12,800	.....

* Fibrinogen derived from clot density values utilizing the formula $F = 18\,d + 120$. (F = fibrinogen in mg./100 cc.; d = clot density.)

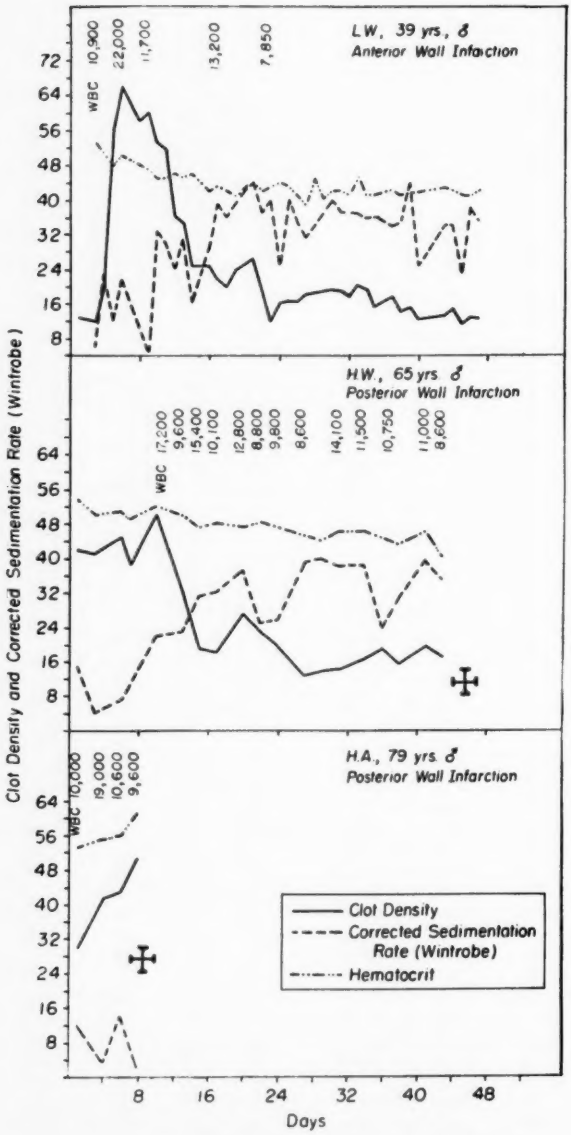
LW, 39 yrs, ♂
Anterior Wall Infarction
WBC 10,900 22,000 11,700 13,200 7,850
HW, 65 yrs ♂
Posterior Wall Infarction
WBC 17,200 9,600 15,400 10,100 12,800 8,800 9,800 8,600 14,100 11,500 10,750 11,000 8,600
H.A., 79 yrs ♂
Posterior Wall Infarction
WBC 10,000 19,000 10,600 9,600
Clot Density
Corrected Sedimentation Rate (Wintrobe)
Hematocrit
Clot Density and Corrected Sedimentation Rate (Wintrobe)
Days

Chart 1.—Marked dissociation between ESR and fibrinogen values in three cases with clinical evidence suggesting massive myocardial infarction. Comparative course of ESR, hematocrit level, and clot density. Fibrinogen is given in milligrams per 100 cc., obtainable from formula $F = 18d + 120$. (F = fibrinogen; d = clot density.)

all mortality during the acute illness was 22% (11 out of 50 cases), the patients with a maximum fibrinogen concentration during the first week of more than 800 mg. per 100 cc. had a mortality rate of 42.1% (8 out of 19 patients), whereas only 3 out of the remaining 31 patients died (9.7%).

Of the 50 patients with acute myocardial infarction studied by us, 15 were women and 35 were men. Five of the 15 women died, representing a considerably higher death rate, of 33.33%, as compared with the corresponding figure of 17.1% (6 out of 35) for the male group. All patients who died were over 60 years old with the exception of two.

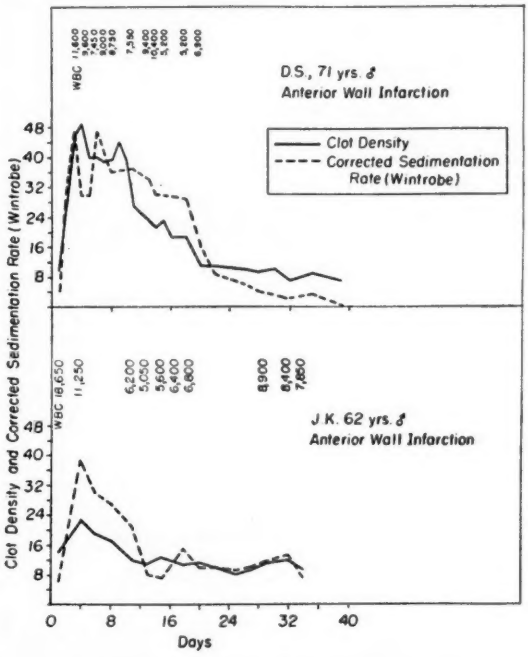

Chart 2.—Comparative course of ESR and fibrinogen values in two cases of myocardial infarction, showing parallelism of both tests. Fibrinogen is given in milligrams per 100 cc., obtainable from formula $F = 18d + 120$. (F = fibrinogen; d = clot density.)

A group of three patients with clinical evidence suggestive of massive myocardial infarction is represented in Chart 1. All three patients had exceedingly high fibrinogen values and high hematocrit readings during the first week of illness, while the sedimentation rate was relatively normal or low. Only after the hematocrit reading declined to values around or below 48 did the ESR rise, thus correlating better with the high fibrinogen level as well as with the clinical status. Patient L. W. (Table), a 39-year-old man, had intractable retrosternal pain during the entire first week of his myocardial infarction, while the temperature was fluctuating between 101 and 102 F. At the height of his illness, when the fibrinogen concentration was 1,308 mg. per 100 cc. and the white blood cell count 22,000, prostration

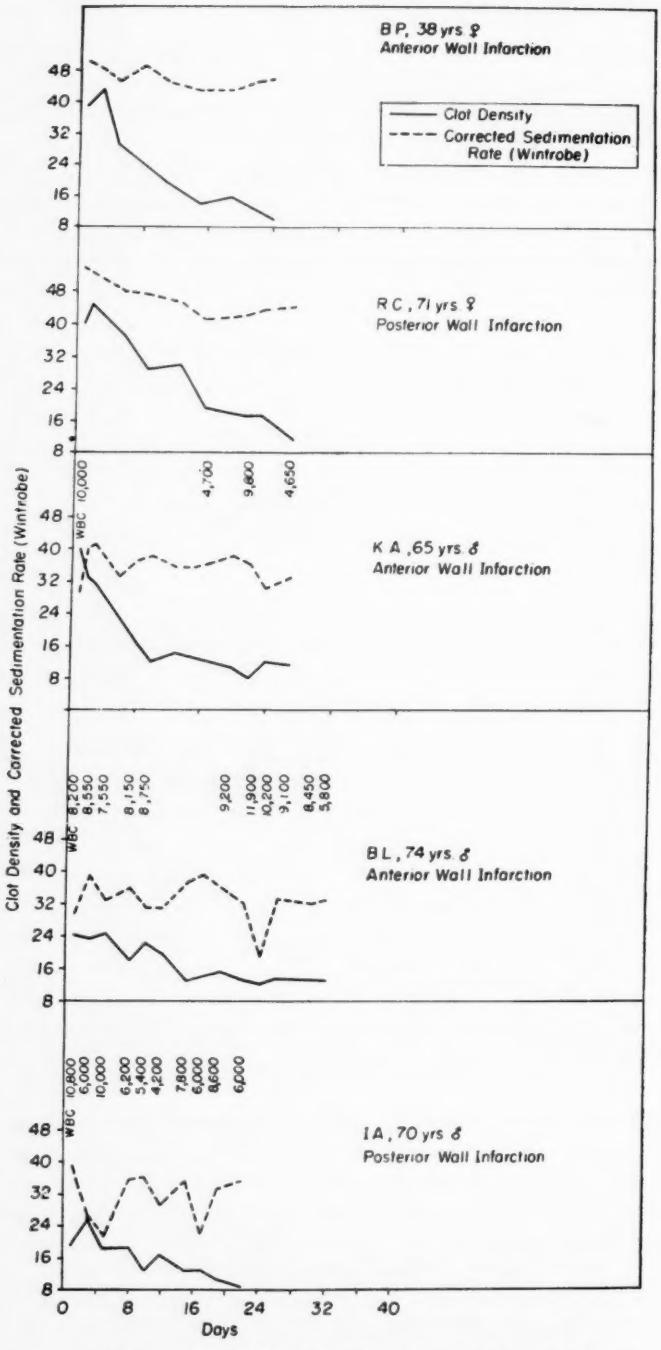

Chart 3.—Dissociation between ESR and fibrinogen values in five cases of myocardial infarction. Early decline of fibrinogen level associated with persistent elevation of ESR. Fibrinogen is given in milligrams per 100 cc., obtainable from formula $F = 18d + 120$. (F = fibrinogen; d = clot density.)

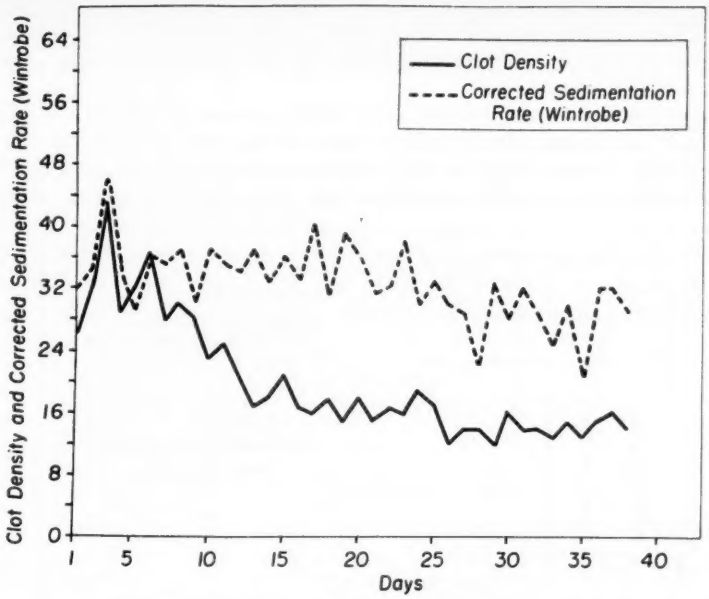

Chart 4.—Mean values of ESR and fibrinogen, expressed in terms of clot density, studied serially in 50 cases of acute myocardial infarction.

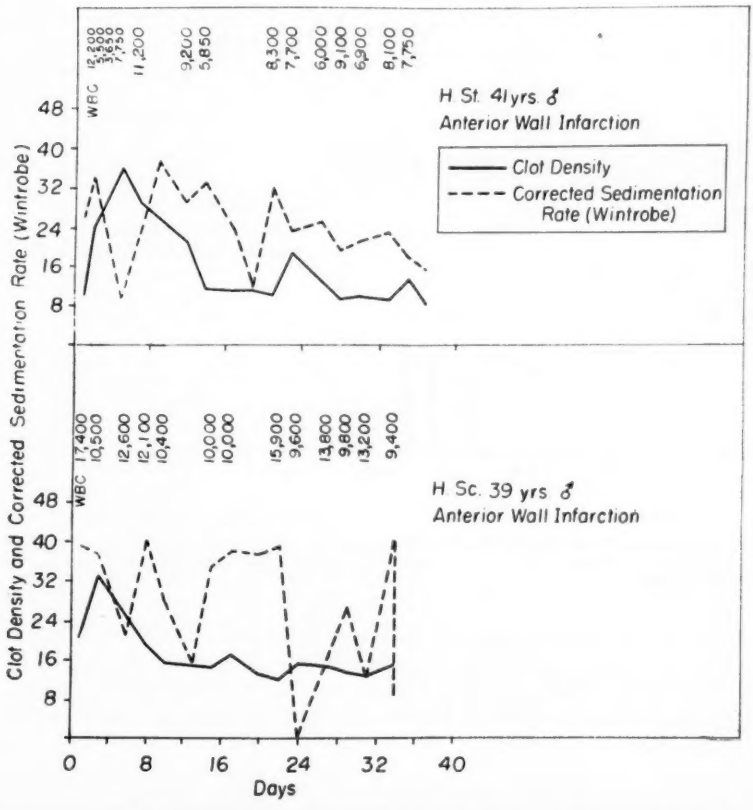

Chart 5.—Erratic course of ESR values in two cases of acute myocardial infarction as compared to early gradual and smooth decline of fibrinogen levels (expressed in terms of clot density).

was pronounced and a very distinct pericardial friction rub was audible at the apex. The maximum ESR during this first week, however, was only 23.

Patient H. W. (Chart 1 and Table), a 65-year-old man, was admitted with a posterior wall infarction. During the early phase of his illness he experienced recur-

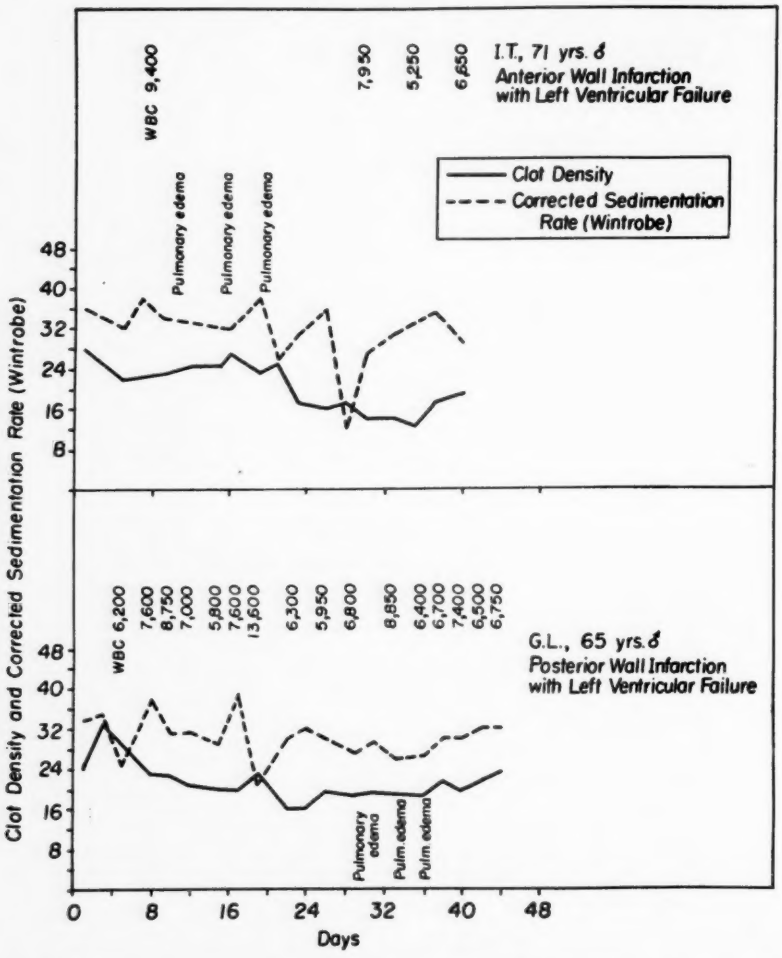

Chart 6.—Persistent elevation of both the ESR and fibrinogen values in two cases of acute myocardial infarction complicated by left ventricular failure (fibrinogen levels expressed in terms of clot density).

rent episodes of crushing retrosternal pain associated with signs of circulatory collapse. The fibrinogen concentration was persistently elevated during this period. The ESR, on the other hand, remained initially low. At the same time the hematocrit reading fluctuated around 50. Only when it declined to 48 did the ESR rise to higher values.

Patient H. A. (Chart 1 and Table), a 79-year-old man with a posterior wall infarction, presented a rapidly declining clinical picture during which the fibrinogen concentration rose steeply to very high levels. The hematocrit readings displayed a tendency to parallel this course. The ESR, however, remained extremely low.

In a few instances the ESR followed the course of the fibrinogen levels quite well, as seen from Chart 2. Patient D. S. (Table), a 71-year-old man, had suffered an acute anterior wall infarction. The course of his illness was characterized by a relatively quick relief from the transthoracic pain which he had experienced during

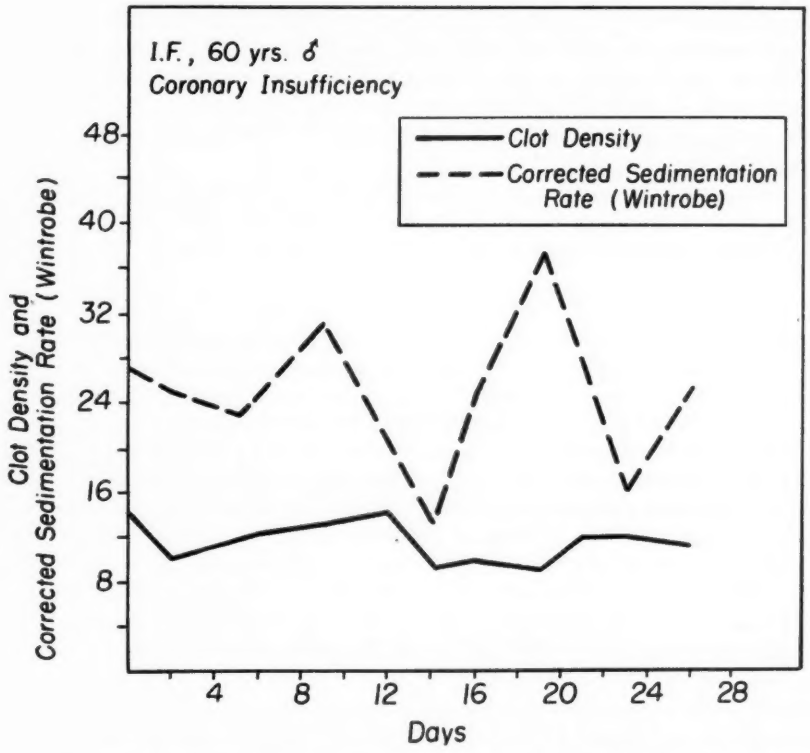

Chart 7.—Normal fibrinogen level in case of coronary insufficiency compared to elevated ESR (fibrinogen expressed in terms of clot density).

the early hours of his illness. Although his condition was aggravated by pneumonia of both lower lobes during the first week, he recovered rather uneventfully. The parallelism between the fibrinogen concentration and the ESR was equally well represented in Patient J. K. (Table), a 62-year-old man with known hypertension, who had suffered an anterior wall infarction but made a rather uneventful recovery. The clinical picture was mild and without complications.

As seen from Chart 3, the ESR in most instances remains persistently at high levels without following the declining course of the fibrinogen concentration. A similar discrepancy is demonstrated in Chart 4, representing the mean values of the

corrected ESR and the fibrinogen concentration expressed in clot density terms and determined over a period of 38 days in all 50 patients observed in this study. After more than five weeks the ESR was still considerably elevated, while the fibrinogen concentration declined to normal levels after the 25th day although in individual cases this decline occurred earlier.

Chart 5 represents two patients, each having sustained an anterior wall infarction. Serial studies disclosed marked fluctuations of the ESR, while the fibrinogen concentration declined steadily to normal. Both patients recovered and were discharged after approximately six weeks.

B. In six patients with left ventricular failure complicating a myocardial infarction the fibrinogen concentration failed to return to normal levels within a three-week period. Although these patients are not included in the Table, two representative cases are shown in Chart 6. Both patients had recurrent episodes of pulmonary edema. Neither the ESR nor the fibrinogen concentration returned to normal values for any length of time.

C. In six patients diagnosed clinically and electrocardiographically as having coronary insufficiency there was no rise in the fibrinogen concentration, while the ESR was frequently elevated as seen, for example, in Patient I. F., Chart 7.

COMMENT

The fact that the ESR is accelerated in acute myocardial infarction has been known since 1931, when Rabinowitz, Shookhoff, and Douglas [1] first reported 10 cases in which the settling of the red blood cells was accelerated for a period of from six weeks to three months after the onset. Similarly, Wollheim [2] also observed that the ESR may be accelerated in coronary thrombosis. Subsequently, this finding has been confirmed repeatedly.¶ Meyers [24] found a complete parallelism between the ESR and the fibrinogen concentration. While in some instances our results also reveal such a parallelism, the mean values of the corrected ESR and the fibrinogen concentration expressed in clot density terms reveal a considerable dissociation (Chart 4). The fibrinogen concentration declines to normal much earlier than the ESR. The days indicated on the abscissae do not necessarily represent the duration of the illness, but the time after the initiation of the serial study. Usually there was a rapid initial rise of the fibrinogen concentration to a maximum value within the first week. In this phase the ESR may follow a similar pattern (Chart 2). In other patients, however (Chart 1), the ESR remained initially normal and began to increase when the hematocrit readings declined. This occurred at the end of the first week or shortly thereafter.

The ESR has long been known to depend also on the volume of packed red blood cells, and corrections have been instituted to allow for the effect of anemia as evidenced by a reduced hematocrit reading.[21] It has been known that an increase in hematocrit level tends to diminish the total fall in the first hour, for it not only slows the rate at which the red cells settle but also prolongs the time before obvious sedimentation begins.# An excessive increase in the hematocrit level to values beyond 48, as occurs in the hemoconcentration which is associated with acute myo-

¶ References 3 through 12.

References 8 and 18.

cardial infarction, has not been taken into account in the standard procedures. The normal values of the ESR in these instances have, therefore, remained unrelated to the clinical course.

In order to study the effect of the high hematocrit readings upon the ESR in instances of a high fibrinogen concentration, we have performed in vitro experiments removing 1 cc. of packed red blood cells from the bottom of a centrifuge tube containing 5 cc. of oxalated blood. The ESR in these cases subsequently showed uniformly high values. This thought was pursued in other experiments in which we have produced high hematocrit readings with specimens of oxalated blood known to have a high ESR and high fibrinogen concentration by removing given quantities of the supernatant plasma. The ESR tended to decline to normal levels when the

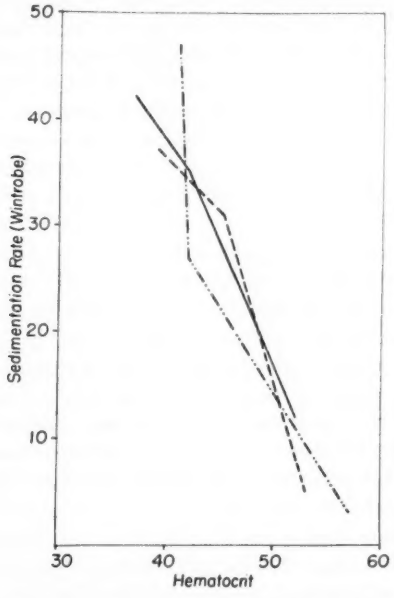

Chart 8.—Relationship between ESR and hematocrit reading. In vitro experiments producing increasing hematocrit readings and decreasing ESR by successive removal of 0.5 cc. of plasma.

hematocrit reading exceeded 48, in spite of a high initial ESR (Chart 8). These experiments seem to offer a valid explanation of the fact that in massive myocardial infarction and in the presence of hemoconcentration the ESR may be normal or low while the fibrinogen concentration is unusually high.

A further cause of the dissociation between the ESR and the fibrinogen concentration lies in the fact that when the fibrinogen concentration increases beyond 700 mg. per 100 cc. the ESR does not follow suit.* Moreover, we have demonstrated a considerable discrepancy between the ESR and the fibrinogen concentration in the early phase of massive myocardial infarction, which probably is due to a high

* References 25 and 26.

hematocrit reading associated with hemoconcentration. It was, therefore, assumed that the fibrinogen concentration could serve as a more adequate clinical indicator of the extent of the myocardial lesion.† Thus, by using the highest fibrinogen concentration during the first week of illness as a criterion it was noted that patients developing a fibrinogen level exceeding 800 mg. per 100 cc. (clot density of 38 or more) were in general more seriously ill than the patients having a maximum fibrinogen concentration below this level. Similarly, the mortality rate among the patients with the higher fibrinogen level was found to be 42.1% (8 patients out of 19), while the corresponding figure in the remaining group was only 9.7% (3 patients out of 31). Death occurred at varying periods of the acute illness. There was no correlation between the time of death and the fibrinogen concentration or the ESR just prior to death. The patients whose maximum fibrinogen concentration exceeded 800 mg. per 100 cc. during their first week of illness also displayed frequently a marked dissociation between the fibrinogen concentration and the ESR, in both the early as well as the later stages of the disease. It is evident, therefore, that the ESR is in no way indicative of the severity of the clinical condition, while, on the other hand, the high fibrinogen concentration seems to mirror more adequately the patient's clinical status as well as the outlook as corroborated from the respective mortality rates. The persistently high ESR so commonly encountered for long periods of time following an acute infarction may possibly be explained by the rise of all globulin fractions occurring in the second week of illness.[28]

The fact that the ESR does not indicate the extent of a myocardial lesion is supported by observations of Selzer, who noted a low or high normal ESR in cases in which the postmortem material showed massive myocardial infarction.[29] It is also borne out by the observations of Riseman and Brown, who state that in their series the "sedimentation indices of the 5 patients who died during the acute attack differed in no way from those of many who recovered."[8] Similarly, Attinger [30] claims that the ESR does not allow any conclusion upon the size of the infarcted area. Gorham and Thompson [10] also note that "no conclusion regarding the severity of the disease, the prognosis in a particular case, or the time when healing occurs can be drawn from the sedimentation rate."

From previous comparative studies of the fibrinogen concentration and the ESR it has been evident that the latter may be considerably elevated in relatively mild inflammatory conditions, such as acute infections of the respiratory or urinary tracts, while the fibrinogen concentration fails to rise or increases only slightly.‡ On the other hand, the presence of necrosis is a most powerful stimulant of fibrinogen production.§ Consequently, in myocardial infarction the fibrinogen concentration reaches very high levels, while the ESR may display values which are similar to those found in infections of the respiratory and urinary tracts.

Some cases studied during the very early phase of the coronary occlusion revealed that the fibrinogen concentration required a period of 24 to 48 hours, during which it increased steeply, to reach the maximum concentration (Patients L. W. and D. S., Charts 1 and 2). In other words, a normal fibrinogen concentration in the very early phase of a myocardial infarction does not necessarily preclude the

† References 24 and 27.

‡ References 22, 27, and 31.

§ References 32 and 33.

presence of a coronary occlusion. Only serial determinations during the following three to four days can help to decide whether occlusion has occurred. The circumstances, therefore, greatly resemble those encountered in electrocardiography, in which positive findings may be absent in the very early phase of an infarction. The fibrinogen concentration, in our experience, does not predict a lesion which will occur but only indicates one which has occurred already. It is nonspecific and represents the body's response to necrosis, but in no way does it foreshadow an occlusive vascular event.

A comparison of the total leucocyte count with both the fibrinogen concentration and the corrected ESR revealed that the number of white blood cells frequently mirrors the severity of a myocardial infarction shortly after its onset. In spite of its significance in the early phase of the disease the total leucocyte count very rapidly recedes to normal within a few days, while the patient is still severely ill.

It can be concluded that in the first stage of a massive infarction the ESR has no significance at all, whereas in most cases it is too sensitive after the first three weeks. The leucocyte count seems to have considerable significance shortly after the onset but is a very crude indicator of the patient's condition later on. The fibrinogen concentration, on the other hand, seems to reflect more accurately the extent of the pathological process during all stages of the illness, as compared with the two other procedures.

Patients with myocardial infarction complicated by left ventricular failure (Chart 6) as evidenced by repeated episodes of pulmonary edema commonly display a moderate elevation of the fibrinogen concentration for prolonged periods of time, while in an uncomplicated case of myocardial infarction the fibrinogen tends to return to normal within a period of three weeks.

In the consideration of the differential diagnosis between coronary insufficiency and myocardial infarction the presence of an elevated ESR is of no significance, because it may be attributable to any concomitant inflammatory condition of the respiratory, gastrointestinal, or genitourinary tract. On the other hand, a persistently normal fibrinogen concentration is strongly suggestive of absence of a necrotizing process and is compatible with coronary insufficiency rather than myocardial infarction. This observation has been of considerable differential diagnostic and prognostic aid in our study. When serial determinations of the fibrinogen concentration performed within one week after the onset of the chest pain have failed to show a rise above 500 mg. per 100 cc. no electrocardiographic evidence of myocardial infarction has been encountered in our material.

A controversy has arisen as to the possible influence of bishydroxycoumarin (Dicumarol) therapy upon the ESR.‖ The fibrinogen concentration, in our experience, however, is in no way altered by the administration of anticoagulant therapy.[22]

Only a small number of the patients reported in this series received anticoagulants. It is of practical importance, however, that, in those instances in which it is decided to treat the patient with hypoprothrombinemic agents, the determination of the prothrombin time with the photoelectric method [23] simultaneously yields the fibrinogen concentration, in the form of the clot density. This in turn allows the evaluation of the clinical status in addition to the estimation of the prothrombin level.

‖ References 34 and 35.

CONCLUSIONS AND SUMMARY

The fibrinogen concentration of the plasma in acute myocardial infarction as studied in 50 cases and determined by the clot density method correlates well with the clinical picture and allows an estimation of the severity of the disease process at the end of the first week. In gravely ill patients an increase of the fibrinogen concentration above 800 mg. per 100 cc. has been observed, while relatively mild cases are usually associated with a moderate elevation. The mortality rate is 42.1% in the first group, while in the latter category the corresponding value is 9.7%.

This differentiation not only is of value, therefore, in determining the severity of a particular case but may also offer a more adequate criterion for the institution of anticoagulant therapy.

The erythrocyte sedimentation rate (ESR), on the other hand, frequently fails to show a close correlation with the clinical condition, particularly in very severe cases, in which it may remain normal or rather low.

While the fibrinogen concentration returns to normal values in most cases at the end of three weeks, the ESR continues to display high values in many instances for a long time after the disappearance of active clinical manifestations.

In six cases of myocardial infarction complicated by left ventricular failure the fibrinogen concentration remained increased for prolonged periods of time.

In six patients with coronary insufficiency the fibrinogen concentration remained normal, while the ESR was either normal or elevated.

When anticoagulant therapy with hypoprothrombinemic agents is administered, the determination of the prothrombin time by the photoelectric method yields the fibrinogen concentration (clot density) without the use of an additional procedure and the clinical course of the patient may easily be followed.

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INFECTIOUS MONONUCLEOSIS AND GUILLAIN-BARRÉ SYNDROME

Report of Three Cases

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DETROIT

THE OCCURRENCE of nervous system involvement as a complication of infectious mononucleosis has been recognized with increasing frequency in recent years. The first report of such an association was by Johansen [1] in 1931; later in the same year Epstein and Dameshek [2] reported a case in this country. In 1950, Bernstein and Wolff,[3] reviewing the literature from 1931 to 1947, found 28 reports, involving a total of 46 patients, with neurologic complications of infectious mononucleosis. They estimated that the incidence of this complication is very low, "certainly not over one per cent, and probably less." This estimate appears justified, as Contratto,[4] in a series of 196 cases, and Milne,[5] with 141 cases, observed no instance of nervous system involvement.

Despite its low incidence, nervous system involvement ranks high among the causes of death in infectious mononucleosis. Lawrence [6] notes that of 16 reported fatalities 7 resulted from neurologic complications. Spontaneous rupture of the spleen and myocarditis accounted for the others.

The types of neurologic manifestations which have been described * fall into four main categories:

(a) Lymphocytic or serous meningitis
(b) Meningoencephalomyelitis
(c) Acute polyradiculoneuritis
(d) Peripheral neuritis

From this it is clear that any part of the nervous system may be affected. There is no evidence to indicate an elective involvement of any particular site. In an analysis by Bernstein and Wolff [3] of 34 reported cases of infectious mononucleosis with definitely proved nervous system involvement, there was a marked preponderance of males over females. In 85% of the cases complete recovery ensued.

In the Henry Ford Hospital 239 cases have been indexed infectious mononucleosis between the years 1925 and 1953. Nervous system involvement was noted

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* References 3 and 7.

in only five cases. In two it took the form of an aseptic meningitis. In the other three cases an acute polyradiculoneuritis of the Guillain-Barré type developed, and these form the subject of this report. This brings to 13 the number of cases of acute polyradiculoneuritis complicating infectious mononucleosis (glandular fever) found in the literature.†

REPORT OF CASES

CASE 1.—R. S. M. (H. F. H. No. 517829), a 24-year-old male clerk, was admitted to the Henry Ford Hospital on Aug. 28, 1947. Three weeks previously he awoke with feverishness, general malaise, headache, sore throat, backache, and anorexia. With the exception of the backache, which subsided within a few days, his symptoms persisted up to the time of admission. He also experienced night sweats and complained of some stiffness of his neck.

Physical examination revealed an acutely ill white man. The temperature (oral) was 101 F., pulse rate 100 per minute, and respirations 16 per minute. A few small nontender cervical nodes were palpated bilaterally. The pharynx and fauces were moderately injected. There was a slight degree of nuchal rigidity. The physical findings were otherwise within normal limits.

Laboratory examination revealed a hemoglobin of 13.9 gm. per 100 cc. and a red cell count of 4,460,000 per cubic millimeter. The leucocyte count was 7,550 per cubic millimeter, of which 25% were neutrophiles, 5% eosinophiles, 2% basophiles, 3% monocytes, and 65% lymphocytes. Eighty percent of the total lymphocytes were of the "atypical," or "leucocytoid," variety, characteristically seen in infectious mononucleosis. Urinalysis was essentially negative. The blood Wassermann test was negative, and the cephalin-cholesterol flocculation was 2 +, thymol turbidity 7 units, and thymol flocculation 2 +. The chest x-ray was essentially normal. On lumbar puncture the cerebrospinal fluid was clear, and the dynamics were normal. There were no cells; the Pandy test was negative; protein was 20 mg. per 100 cc., and sugar, 69 mg. per 100 cc. Routine cultures of the blood and cerebrospinal fluid yielded no growth. The blood heterophile agglutination test was negative on Aug. 30 and again on Sept. 10.

The hospital course was uneventful. The temperature, which was consistently elevated to from 99 to 100 F. during the first hospital week, returned to normal in the second week. The patient became asymptomatic and was discharged on Sept. 10 with a diagnosis of infectious mononucleosis.

On Sept. 27 the patient returned, reporting that for two weeks weakness had gradually and progressively developed, first in the legs, then in the back, arms and face, bilaterally, associated with prickling sensations in the fingers and feet. He had become unable to raise the arms over his head or to stand unassisted. Severe frontal and occipital headache occurred when sitting up and was relieved by lying down.

On examination the temperature was 99.8 F., pulse rate 104 per minute, and respirations 18 per minute. The liver edge was palpated 2 cm. below the costal margin and was slightly tender. There was slight resistance and complaint of pain on passive flexion of the neck. There was mild ptosis and marked weakness of all facial muscles bilaterally. There was moderate weakness of the muscles of all four extremities, with more involvement of flexor than of extensor groups, and weakness of the back muscles. The tendon reflexes in all extremities were almost totally absent; the abdominal, cremasteric, and plantar reflexes were normal. The muscles of the upper arms and lower legs were tender to pressure. There was slight diminution of light touch, superficial pain, and thermal sensibility over the feet and mild diminution of vibratory and position sense in the fingers and toes bilaterally.

Lumbar puncture performed on Sept. 28 revealed an initial pressure of 40 mm. of water, unaffected by jugular compression, and a terminal pressure of 0 mm. of water after collection of 2 cc. of fluid. The cell count was 2 leucocytes per cubic millimeter and the Pandy test was negative.

A repeat spinal puncture on Oct. 1 revealed an initial pressure of 195 mm. of water, with normal dynamics. The cell count was 3 leucocytes per cubic millimeter, Pandy test 1 +, protein 88 mg., sugar 60 mg., and chlorides 727 mg. per 100 cc., and the colloidal gold test was negative. Routine spinal fluid culture was negative for pathogens.

† References 8-15.

Other laboratory data at this time were as follows: urinalysis normal; blood heterophile agglutination test negative; hemoglobin 15.4 gm. per 100 cc. The blood leucocyte count was 6,400, with 60% neutrophiles, 1% eosinophiles, 2% basophiles, 31% lymphocytes (no "atypical" forms noted), and 6% monocytes. The cephalin-cholesterol flocculation was 1 +, thymol turbidity 5 units, and thymol flocculation 4 +.

This hospital course was without complications. Improvement commenced a few days after admission, and a moderate return of muscle strength was apparent in all the involved groups by the time of discharge, on Oct. 9, 1947.

Two weeks later some muscle weakness was noted, but the patient could walk unaided and could use his arms and hands without difficulty. The tendon reflexes were almost completely absent.

The patient failed to keep subsequent outpatient appointments and shortly thereafter moved to another city. When last heard of, in November, 1948, he was still complaining of profound fatigue.

CASE 2.—W. J. G. (H. F. H. No. 694730), a 16-year-old white male high school student, was admitted to the Henry Ford Hospital on Oct. 23, 1952. The history, obtained from his parents, revealed that he had been in good health until about three weeks previously, when, after a few days of general malaise, abdominal pain, fever, generalized glandular enlargement, and transient mild jaundice developed. He was treated in a local hospital, where the diagnosis was made of infectious mononucleosis.

One week after the onset of this illness he noticed weakness, numbness, and tingling of his upper and lower extremities and a gradually increasing unsteadiness of gait. Some days later difficulty in swallowing and speaking developed, and these symptoms had shown steady progression up to the time of his admission here.

Physical examination revealed a well-developed thin white youth, appearing apprehensive and acutely ill. Speech was thickened and slurred, and swallowing was accomplished with difficulty. The oral temperature was 98 F., blood pressure 120/80, pulse rate 100 per minute, and respirations 20 per minute. The cervical, axillary, and inguinal lymph nodes were moderately enlarged, discrete, and tender. The heart was not enlarged; the rhythm was regular, and no murmurs were noted. The lungs were clear to percussion and auscultation. The liver and spleen were not palpable. Bilateral ptosis was observed, but the pupillary reactions and extraocular movements were normal. There was almost complete absence of the gag reflex, marked weakness bilaterally of the muscles of expression, and moderate weakness of the muscles of mastication. Diaphragmatic excursion was normal, but there was marked weakness of the lower intercostal muscles bilaterally. Examination of the extremities revealed marked weakness of all muscle groups, diminished to absent tendon reflexes, and a moderate degree of muscle tenderness. A questionable Babinski reflex was obtained on the right. Sensory changes were confined to the distal areas of the extremities and consisted of moderate impairment of pain, temperature, and touch sensation, shading off to normal just below the elbows and knees, and a marked dimunition of position sense in the toes. Nuchal rigidity was present, and a positive Kernig sign was elicited.

Laboratory examination revealed a leucocyte count of 14,350 per cubic millimeter, of which 55% were neutrophiles, 8% band forms, 1% eosinophiles, 2% basophiles, 8% monocytes, and 26% lymphocytes. More than half of the lymphocytes were "leucocytoid." The hemoglobin was 14.0 gm. per 100 cc., and erythrocytes were 4,540,000 per cubic millimeter. Urinalysis was essentially negative. The heterophile agglutination test was positive in a dilution of 1:1,792. The blood Wassermann test was negative, the cephalin-cholesterol flocculation was 3 +; thymol turbidity, 5 units, and thymol flocculation, negative. The quantitative bilirubin values (van den Bergh test) were reported as 0.2 mg. (direct) and 1.28 mg. (total) per 100 cc. The fasting blood sugar was 98 mg., and the nonprotein nitrogen 46 mg., per 100 cc. The cerebrospinal fluid was clear, with normal dynamics, and contained 280 mg. of protein per 100 cc. There was a 2 + Pandy reaction; no leucocytes were present, and the sugar was 83 mg. per 100 cc.

The patient's hospital course was stormy. He became incontinent of urine and feces. The weakness of the extremities progressed to complete quadriplegia. Increasing dysphagia necessitated tube feeding, and frequent aspiration was required to clear the mouth and pharynx of accumulated secretions. On the fourth hospital day, owing to increasing respiratory embarrassment, he was placed in a tank respirator, where he remained for 12 days. During this time there

occurred two episodes of atelectasis of the lower lobe of the right lung, requiring bronchoscopic removal of thick mucous plugs. On the seventh hospital day neurologic involvement was maximal, and thereafter a gradual improvement occurred, sufficient to permit his discharge from the hospital on Dec. 24. At that time there remained slight weakness of the facial muscles, of the flexors and extensors of the elbows, and of the pretibial and peroneal muscles of the right leg. There was a more pronounced residual weakness of the peroneal and anterior and posterior tibial muscles of the left leg, with a foot drop.

During most of the hospital stay the temperature had remained normal. For one week, from Oct. 25 to 31, it had spiked daily to 102 F. (rectal). Tachycardia, with a rate of 100 to 120, had been present almost constantly during the first four weeks.

The blood heterophile agglutination test, positive on admission in a dilution of 1:1,792, was one month later positive in a dilution of 1:224. On Dec. 1, 1952, the cerebrospinal fluid was free of cells, with 146 mg. of protein per 100 cc, 73 mg. of sugar per 100 cc., and a 1 + Pandy reaction. A heterophile agglutination test performed on the cerebrospinal fluid was reported as positive. On Dec. 4 the cephalin-cholesterol flocculation test was 1 +, thymol turbidity 2 units, and thymol flocculation negative. On Dec. 8 a 5 mg. sulfobromophthalein (Bromsulfalein) test showed no retention in 45 minutes. The van den Bergh findings had likewise returned to normal. A differential leucocyte count on Dec. 1 showed 30% normal lymphocytes and 9% "leucocytoid" forms.

After leaving the hospital, the patient continued regular supervised exercises. When last seen on Jan. 22, 1953, some further improvement had taken place, although a brace was still required for walking.

CASE 3.—H. J. H. (H. F. H. No. 540564), a 50-year-old white man, was first seen in the diagnostic clinic of the Henry Ford Hospital on May 21, 1948, regarding inguinal hernia. Hernia repair was done on July 9, 1948, with the use of local anesthesia. The postoperative convalescence was uncomplicated.

On July 21 the patient returned, complaining of cramping pains, numbness and tingling in the feet, spreading gradually to the level of the knees, "strange" sensations in the hands, nausea, vomiting, headache, and substernal pain, of two days' duration.

On physical examination the temperature (oral) was 98 F., pulse rate 84 per minute, respirations 24 per minute, and blood pressure 160/90 mm. Hg. No significant lymphadenopathy was noted. There was a slightly enlarged, nontender liver.

On neurological examination the patient was somewhat apprehensive. His speech was a little thick. Motor cranial nerves were intact. There was no neck rigidity. Muscle strength in the arms was good. The lower extremities showed slight weakness in flexion of the hip and in flexion and extension of the knee on the right; there was moderate weakness of all movements of the right ankle and very slight weakness of the left ankle. The extensors and flexors of the toes were very weak on the right and slightly weak on the left. Position sense was intact, as was pressure-pain sense at the Achilles tendons. There was no muscle tenderness. All deep reflexes and the plantar reflexes were absent.

Laboratory examinations revealed a hemoglobin of 13.3 gm. per 100 cc., erythrocytes 4,140,000 per cubic millimeter, and leucocytes 11,300 per cubic millimeter, with differential values of 55% neutrophiles, 1% eosinophiles, and 35% lymphocytes. Urinalysis and the blood Wassermann test were negative. The blood heterophile alggutination test was negative. The spinal fluid was clear and colorless under normal initial pressure, with a normal Queckenstedt response. Spinal fluid examination yielded a cell count of 7 erythrocytes; negative Pandy, Kolmer, Kahn, and Eagle tests; a colloidal gold (Lange) curve of 0122100000, and 70 mg. of sugar, and 35 mg. of protein per 100 cc.

On July 23 there developed weakness of the right side of the face involving all facial muscle groups. On the following day this involved both sides of the face and there was also some difficulty in swallowing. There was some suggestion of bilateral external strabismus. The patient complained of difficulty in breathing, but full deep inspiration was still possible on command. The patient's condition was considered critical. On July 24 he became cyanotic and was placed in an oxygen tent, with immediate improvement. Motion of the diaphragm had continued to be good. Hot packs were applied to the lower extremities for a complaint of pain in the knees.

On July 24 the temperature and pulse and respiration rates, which hitherto had been normal, showed slight elevation, and on each subsequent day the temperature reached an evening peak, up to 101.8 F., gradually subsiding after three days. The spinal fluid protein was 85 mg. per 100 cc. on July 20 and 101 mg. per 100 cc. on July 27. The patient continued to be apprehensive and irritable and vomited occasionally. Breathing was not definitely embarrassed, although of small excursion, and the patient was content to remain out of the oxygen tent. Liquids were swallowed satisfactorily.

Neurological examination on July 30 revealed a moderate bilateral ptosis, marked weakness of the right facial muscles and moderate weakness of the left facial muscles, marked weakness of all muscles of the right arm and moderate weakness of the left arm, complete absence of all voluntary power in the right lower extremity and almost total loss in the left lower extremity, absence of all deep reflexes in the arms and legs, and almost total absence of plantar reflex in each foot. Position sense was slightly impaired in the fingers of the right hand and absent in both feet. Vibratory sense was lost at the malleoli at both ankles. Light touch sensation was absent over the outer aspects of both legs and was much diminished in the outer aspects of both thighs. Superficial pain sense was markedly impaired in the feet but normal in the legs, and temperature sense was intact throughout. All muscles of the thighs were moderately tender, and the leg muscles were markedly tender to compression.

A second test for blood heterophile agglutination, on July 30, was negative. The patient was transferred to a Veterans Administration Hospital on the same day. Reports were subsequently received from the Veterans Hospital of positive blood heterophile agglutination of 1:448 on Aug. 12 and Aug. 26 and of 1:224 on Aug. 31.

COMMENT

The diagnosis of infectious mononucleosis was made in Case 1 on the basis of the typical blood picture, despite the failure on two occasions to demonstrate the presence of sheep hemagglutinins in the blood. Gardner and Paul,[16] in a series of 81 infectious mononucleosis patients seen between the years 1938 and 1946, found that the highest incidence of positive heterophile agglutination tests occurred in the second week of the disease and that even then the antibodies failed to develop in 40% of patients. According to their observations, during the first week and after the third week of the illness a positive heterophile agglutination might be expected in less than 50% of patients. Although these figures suggest a lower incidence of heterophile antibody development than is generally accepted, we feel that failure to demonstrate agglutinins does not invalidate the diagnosis in the presence of a compatible clinical picture and a characteristic blood smear.

In Case 2 sheep hemagglutinins were demonstrated in the cerebrospinal fluid, using the method described by Silberstein and co-workers.[17] A 4+ agglutination occurred with 1 cc. of cerebrospinal fluid and 3+ with 0.5 cc. After absorption with guinea pig kidney antigen a 3+ agglutination was obtained.

In Case 3 the absence of a positive heterophile reaction and the normal appearance of the blood smears precluded an initial diagnosis of infectious mononucleosis. However, the subsequent development of a rising heterophile titer in the absence of serum injection makes the diagnosis feasible. Unfortunately, no blood cell count was available at the time of the rising heterophile titer.

Natural agglutinins (antibodies) to sheep erythrocytes are present in sera of practically all persons. They are called heterophile agglutinins, because they are not the type produced by injection of sheep erythrocytes, the homologous antigen. Their origin is unknown. They are found in low titer (1:7 to 1:56) in 80 to 90% of normal persons and may occasionally occur in higher dilutions. Three types of

sheep hemagglutinins may be present in the serum of man (Table) and may be distinguished by differential absorption tests.‡

Since a Forssman antibody is one produced by injection of guinea pig organs into rabbits and is absorbed by a suspension of guinea pig kidney, the agglutinin associated with infectious mononucleosis is not a true Forssman antibody. The differential absorption tests are indicated clinically in patients with sera showing borderline values or in whom the clinical picture requires differentiation of serum sickness and infectious mononucleosis.

It has also been noted [23] that the titer of agglutination is dependent to a degree on the particular erythrocyte suspension used. Suspensions from different sheep vary considerably in the ease with which they agglutinate on exposure to a given serum. Another possible source of error is that cold agglutinins for sheep erythrocytes may be present in the serum of patients with infectious mononucleosis and other disorders.[24] This factor, however, may be eliminated by simply rewarming the test tubes.

The syndrome of accute polyradiculoneuritis accompanied by a marked increase in protein in the cerebrospinal fluid without a corresponding increase in cells was described in 1916 by Guillain, Barré, and Strohl.[25] The diagnostic triad stressed by

Differential Absorption of Sheep Hemagglutinins Present in Human Serum

Sheep Erythrocyte Heterophile Agglutinin	Absorbed by Guinea Pig Kidney	Absorbed by Boiled Beef Erythrocytes
Associated with normal sera	+	−
Associated with serum sickness	+	+
Associated with infectious mononucleosis	−	+

these writers was (1) the albuminocytologic dissociation in the cerebrospinal fluid, (2) preponderance of motor weakness over the signs of sensory disturbance, and (3) the favorable prognosis, usually with complete recovery. In 1936 Guillain [26] again stressed the importance of the rise in the spinal fluid protein, giving 1,000 to 2,000 mg. per 100 cc. as the usual finding. However, in the following year (1937), at a symposium on radiculoneuritis in Brussels, he withdrew many of his previous diagnostic criteria.[27]

It is now conceded that the hyperalbuminosis of the cerebrospinal fluid may frequently be absent during the early stages of the disease and that its occurrence, in all probability, is dependent on purely local factors, such as vasodilatation and a partial block to the drainage of spinal fluid from edema and swelling of the inflamed nerve roots.

It is also felt that the outcome is not invariably benign. In 126 cases collected from the literature by Fox and O'Conner [28] there were 26 fatalities. In a masterly review of the subject, Haymaker and Kernohan [11] conclude that there is no essential difference between the radiculoneuritis of Guillain, Barré, and Strohl and Landry's paralysis. They suggest the name Landry-Guillain-Barré syndrome, to emphasize the possibility of a fatal outcome.

The etiology of the condition remains an enigma. It is unknown whether or not all cases are due to a single etiologic agent, and, even if so, the nature of the agent is open to surmise. Much of the evidence supports an infectious etiology, possibly

‡ References 18-22.

a virus. Frequently there is a history of a preceding illness, often a mild upper respiratory infection. In the Henry Ford Hospital 34 cases of the Guillain-Barré syndrome were encountered in the 10-year period of 1943 through 1952. In four cases the illness was preceded by a "cold," three cases followed a sore throat; in two there was a history of the "flu"; one followed an acute gastroenteritis, and three were associated with infectious mononucleosis. In the remaining 22 cases there was no history of preceding illness.

SUMMARY

The occurrence of nervous system involvement as a serious complication in a small percentage of cases of infectious mononucleosis is stressed.

Three such cases are reported, in which the neurologic manifestations took the form of an acute polyradiculoneuritis.

Sheep hemagglutinins were demonstrated in the cerebrospinal fluid in one case.

The heterophile agglutination test in the diagnosis of infectious mononucleosis is discussed, and some difficulties are mentioned.

The nature of the Guillain-Barré syndrome is discussed briefly.

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Progress in Internal Medicine

CARDIOVASCULAR DISEASES

A Review of Some Significant Publications (July 1949-June 1952)

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THE THREE years of cardiovascular literature encompassed by this report have witnessed a steady advance in the development of new techniques and promising agents for the recognition and the relief of cardiovascular disorders. The following review of these contributions, representative rather than inclusive, has been arranged under 10 main headings.

I. CONGENITAL HEART DISEASE

The fundamental causes of congenital heart disease continue to excite investigation and speculation. Maternal rubella, established beyond dispute as a prime cause of congenital defects, has, according to Swan,[1] three chances out of four of resulting in a congenitally defective infant if contracted during the first four months of pregnancy. The critical period for the development of cardiac defects is from the fifth to the eighth week of intrauterine life, during which time the septa are forming, the bulbus cordis is undergoing involution, and the torsion of the great vessels is taking place. There is no definite evidence that convalescent serum or gamma globulin favorably affects the course of the illness in the exposed woman, and the best prophylaxis remains active immunization with the virus before the childbearing age. Although dubious of Swan's striking figures, Neel [2] nevertheless feels that the risk of a congenital defect from rubella during the first four months is not below 30 chances in 100, or approximately equal to the chances for diseased offspring where any dominant heredity is involved. Both authors agree on the available evidence that therapeutic abortion is justified if rubella is contracted during the first four months of pregnancy. In a study of 250 cyanotic and 50 acyanotic children with congenital heart disease for possible genetic and environmental etiologies of their disease, Campbell [3] could detect no environmental factor of significance other than rubella and this appeared to be responsible in only four instances. The author concluded that the causes of congenital heart disease are chiefly genetic, basing this observation on the fact that, although not common, the occurrence of other instances of congenital cardiac defects in siblings and distant relatives was more frequent than could be expected by chance. Ingalls,[4] on the other hand, on the basis of embryological and epidemiological studies, emphasizes that environmental factors such as infection, anoxia, and possibly deficiency states may be quite as important in determining congenital defects as any hereditary factor. He particularly stresses stage specificity: "A single inciting agent may give rise to many different kinds of malformation, the particular type being determined by the age of embryonic development at which the injurious agent acts." Support of this concept

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is provided by the work of Warkany,[5] who deprived pregnant female rats of certain essential nutritional elements. In these studies vitamin A deficiency was particularly effective in producing cardiac anomalies. It is unlikely, however, that deficiencies occur often enough in the United States to account for a significant number of the congenital cardiac defects observed.

The fact that children with cyanotic congenital heart disease frequently tolerate relatively low degrees of oxygen saturation of the blood without any noticeable effects on the intelligence or on the state of consciousness when at rest has led Adams and Hansen [6] to study the possible role of carbonic anhydrase in the blood of these children. Comparison of 18 of these cyanotic children with 6 children with congenital heart disease of the acyanotic type, 13 normal newborn infants, and 27 children with no cardiac disease, varying in age from one week to 20 years, showed that all the cyanotic children had elevated carbonic anhydrase levels as compared with the rest of the group, including the acyanotic ones. When allowance was made for the increased hematocrit level in the cyanotic group, however, there remained no significant difference between the two groups.

Of considerable theoretical diagnostic interest, albeit forbidding in practice, is the report of Ponsdomenech and Beato Núñez * of 45 trocar punctures of the heart in 30 patients without mortality or untoward results. Five of the patients subsequently succumbed to their primary illness (carcinoma of the lung with metastases) at varying times following the cardiac puncture. At postmortem examination no evidence whatever could be found of the puncture in the pericardium, myocardium, or endocardium of four of the patients. In the fifth patient, who died seven days after the puncture, there were found small blood clots in the pericardial sac in a reabsorbing stage. By introducing iodopyracet (Diodrast) through the trocar, the authors obtained x-ray films of "perfect clearness," with a density and precision in the left ventricle and aortic areas more accurate than those obtained by the usual angiocardiographic methods. In most of the patients in whom the left ventricle was injected there was "magnificent visualization of the coronary arteries." Despite the obviously excellent results, a certain reluctance at this time in attempting to confirm these findings would be understandable.

The association of brain abscesses (usually solitary) with congenital intracardiac shunts has been emphasized by Maronde.[9] Eleven acceptable examples of this syndrome were found in a series of 13,883 autopsies. The congenital cardiovascular shunts in this series numbered 81. The author supports earlier suggestions that two factors favor the formation of these abscesses: previous injury to the cerebral tissue, as from paradoxical septic or sterile emboli, and the shunting of blood into the systemic arterial vessels without the benefit of the filtering action of the pulmonary capillaries. The observations of Berthrong and Sabiston [10] on cerebral lesions in congenital heart disease suggest perhaps an additional explanation to that of paradoxical emboli. These workers found cerebral thrombosis in 13 out of 62 cases of tetralogy of Fallot coming to autopsy. In these cases with high hematocrit levels, any cause leading to increasing polycythemia, endothelial damage, or decreasing blood flow may result in prompt intravascular thrombosis. Thrombosis in situ in the cerebral vessels seems as reasonable a possibility as paradoxical emboli or those from mural thrombi in the heart chambers to predispose cerebral tissue to infection.

* References 7 and 8.

Sancetta and Zimmerman [11] agree that as a specific bacterial cause of death in patients with congenital heart disease, brain abscess is second only to bacterial endocarditis.

Reporting a series of 33 patients with but one death, Kerr and Sodeman [12] have sounded an optimistic note on the association of congenital heart disease and pregnancy. Not only was mortality low, but congestive cardiac failure occurred in only four patients as a result of pregnancy. In the total of 80 pregnancies in this group, only 10 were accompanied by toxemia, in four different patients, a rate of 12% and well below the previous alarming figure of 33% reported by Lund in 1948. Moreover, in the woman who died, toxemia appeared to be a principal factor in her demise, and a special effort to prevent toxemia in this type of patient seems necessary. The authors allude to the fact that the placenta functions as an arteriovenous shunt and is therefore equivalent to the temporary addition of another congenital anomaly. Nevertheless, in the 21 patients in the group who had one or another of the various forms of congenital arteriovenous communications, only one showed vascular collapse at the time of delivery, and, as noted above, this patient was also toxemic. In patients with coarctation the authors advise Caesarian section to relieve the additional blood pressure elevations occurring in active labor. An interesting case of truncus arteriosus communis compatible with full term pregnancy at age 19 has been reported by Simon and Lustberg.[13] Unfortunately the patient died suddenly of pulmonary embolus on the third postpartum day. Autopsy showed that her pulmonary arteries took origin from the descending aorta, as is usually found in persons with this condition who reach maturity. The infant appeared normal and survived. In another report, on a patient who survived to the age of 38 with transposition of the large vessels, the second oldest patient with this anomaly reported in the literature, Messeloff and Weaver [14] note that the patient had carried a stillborn fetus to full term at age 23, without, so far as could be determined by her history, any symptoms of congestive heart failure nor increase in her usual cyanosis and dyspnea.

Congenital absence of the pulmonary artery, an anomaly previously not classified in current nomenclature, has been described by Manhoff and Howe.[15] These authors emphasize the difference between this anomaly and atresia of the pulmonary artery, the difference being that in the former the primary cause is an absence of the primitive sixth aortic arch. Cyanosis was not as marked as in an ordinary tetralogy of Fallot, inasmuch as the bronchial arteries developed to an unusual degree, permitting some oxygenation of the blood. Criteria for the diagnosis of Ebstein's anomaly of the tricuspid valve have been established by Engle and her co-workers.[16] In this anomaly the leaflets of the tricuspid valve are fused into a membranous structure which extends down into the cavity of the right ventricle, separating the latter into a proximal and distal chamber, the proximal portion being anatomically and functionally continuous with the right auricle. In most cases the foramen ovale is patent. Although the clinical and laboratory findings which now make possible the diagnosis of this condition in life are too detailed for inclusion here, the significance of the condition lies in the fact that to date no surgical means exist for its correction. Consequently it is of considerable importance to distinguish Ebstein's anomaly from tetralogy of Fallot or valvular pulmonary stenosis, both of which may be markedly improved by surgical intervention.

The literature on the surgery of congenital heart disease has become so extensive that it is not possible within the confines of this paper to do more than refer briefly to some of the more interesting features. For a concise review of both the pertinent experimental data and the practical clinical applications, together with a voluminous bibliography, the interested reader is referred to the Lederle Bulletin of May 1952.[17] In another pithy review Hanlon [18] comments on the two most serious deterrents to definitive repair of cardiovascular defects. The first, the factors responsible for failure of most tissue grafts from one patient to another, continues to elude explanation, although the use of arterial grafts seems thus far successful. The second, the necessity of maintaining the pumping action of the heart and the oxygenating function of the lungs during cardiac surgery, is being approached along a number of paths by the development of various types of pumps which may be substituted for the heart. To date, however, these mechanical pumps remain too intricate and cumbersome for ready use. A recently developing alternative approach is therefore of tremendous interest. Hegenauer and his associates [19] have demonstrated that dogs made hypothermic, to a temperature of 16.2 C., which is near fatal temperature, can be successfully rewarmed with complete restoration of all changes in pulse, blood pressure, electrocardiogram, and other observations occurring during the period of cooling. It seems likely that this complete reversibility is dependent upon reduction of the metabolic rate and oxygen requirement of all tissues owing to the reduction of temperature. Under such conditions of hypothermia, Bailey and his associates † have demonstrated the feasibility in dogs of occluding the great vessels and opening the heart to perform virtually bloodless operations under direct exposure, subsequent to which the dogs recovered without apparent ill effects. More recently, in a human infant aged 5 months these workers lowered the body temperature to 90 F. (rectal) and successfully accomplished the Brock procedure for pulmonary stenosis, usually a risky operation at this age. During hypothermia in this case the heart rate, despite surgery, dropped from 100 to 70, and cardiac irritability was greatly reduced. If further knowledge and control of low body temperature techniques are found to permit prolonged direct approach to human intracardiac structures, the prospect for further surgical triumphs seems virtually limitless.

Experience with 412 surgically treated patients with patent ductus arteriosus has been summarized by Gross and Longino,[20] who recommend suturing as well as ligation in all cases. Where no complication exists prior to surgery, the mortality has been under 0.5% in their experience. While it is possible to argue that correction should be reserved for specific indications, such as retardation in growth; cardiac fatigue, embarrassment, or failure, and the presence of blood stream infection, it is the authors' contention that all patients with this condition should be operated upon, both because of the increased likelihood of eventual infection of the ductus and the demonstrated reduction of life expectancy in the untreated adult to about one half that of the population as a whole. Stressing the importance of this defect in infants, Ziegler [21] disputes the commonly held opinions that patent ductus cannot be easily diagnosed much below the age of 3 years and that even if diagnosis is made operation should probably be postponed anyway. Contrary to the foregoing opinions, the author found that, except in the presence of a complicating pulmonary

† McGuire, J. J.: Personal communciation to the author.

hypertension, a continuous murmur was invariably present by the age 18 months; it was found in one infant as early as 6 weeks of age and in another at 5 months. All the infants had at least a systolic murmur, which occurred alone more commonly than with a diastolic component under the age of one year. Detailed clinical and laboratory criteria for the diagnosis of patent ductus in infants are set down, including cardiac catheterization and angiocardiography. In the author's experience, indications for operation, as judged by the incidence and degree of cardiac enlargement and the occurrence of congestive failure, appear to be more urgent in early infancy than at practically any other age. Emphasis is placed on the observation that, even with careful medical management, sudden and fatal pulmonary edema may not be preventable in infancy. Believing the mortality rate of untreated patent ductus to be high in infancy relative to the operative mortality on such patients (out of a group of 22 patients 3 years old or younger one infant died of failure prior to operation and another died during induction of anesthesia; the remaining 20 survived surgery), Ziegler urges that serious consideration be given to the establishment of the diagnosis of uncomplicated patent ductus in all infant congenital heart disease and that, where demonstrated, the lesion be surgically corrected at an early opportunity. Illustrative of the occasional atypical case of patent ductus are the two patients reported by Myers and his associates,[22] who lacked both the characteristic continuous murmur and, by catheterization, the usual aortic-pulmonary pressure gradient. In the second patient the catheter passed by chance directly from the pulmonary artery into the aorta, permitting direct readings of aortic pressure. Both patients were shown to have pulmonary artery hypertension, with mean pressures nearly approaching those of the aorta. As a consequence there was minimal flow from the aorta through the ductus into the pulmonary artery during diastole, and this in turn explained the absence of a continuous murmur during diastole, as well as the lack of a high systemic pulse pressure. In the second case lung biopsy at the time of operation showed definite vascular abnormalities, which served to underline the point that surgical correction should be carried out before irreversible vascular changes occur in the lungs. Johnson and his co-workers [23] in this connection have presented the case of a woman who experienced intermittent right to left shunting through a patent ductus as a late complication of her disease, confirmed by pressure measurements and blood oxygen values obtained shortly before her death. It is presumed that as this patient grew older the prolonged increase in pulmonary blood flow eventually resulted in pulmonary hypertension. This together with natural aging processes resulted in further pulmonary vascular resistance and increasing pulmonary hypertension, until finally a state of balance was reached in which it was possible for a temporary reversal of flow through the ductus to occur with slight exertion, with resultant transitory cyanosis. At autopsy three so-called "impingement plaques" were noted in the wall of the aorta just opposite the aortic opening of the ductus, which were presumably due to the high velocity of the jet of blood striking the wall of the aorta. The authors feel that, even where such partial reversal of flow can be demonstrated, ligation of the ductus would result in marked reduction of both the pulmonary blood flow and pulmonary hypertension and would therefore be beneficial.

The results of operations for relief of cyanosis in 1,000 cases of tetralogy of Fallot and/or pulmonary stenosis have been recorded by Taussig and her associates [24] and show that there is an 85% chance of coming through surgery greatly

improved, with an equally good chance of maintaining that improvement thereafter. Once the patient has recovered from operation, the additional anomaly created by the operative shunt does not appreciably increase the patient's susceptibility to subacute bacterial endocarditis. The immediate mortality of the entire group was 15.6%, being less for patients with tetralogy of Fallot than for those with other malformations associated with pulmonary stenosis or atresia. Although conceding that good results may be obtained with the shunt operation for pulmonary stenosis, both Brock [17] and Bailey and his colleagues [17] consider that a direct attack upon pulmonary or infundibular stenosis is preferable if at all feasible surgically. Bahnson and Ziegler [25] report 15 fatal cases of congestive failure in 500 cases in which the Blalock procedure was performed. Ten of these patients died a few hours postoperatively of pulmonary edema. The remaining five survived varying periods from 3 to 67 months and showed chronic passive congestion. Another case of cardiac failure after aortic-pulmonary anastomosis is reported by Sheedy and his associates.[26] In this instance, although anoxia was relieved by the operation, the presence of an atrial septal defect, together with the increased work load of the induced shunt, presumably exhausted the remaining cardiac reserve. Leininger, Gibson, and Potts [27] have described postoperative observations on their series of 214 children with congenital pulmonary stenosis. There was a 10% mortality in the 199 children in whom a shunting operation was performed. In an anatomic study of 48 hearts with the tetralogy of Fallot to determine the types and incidence of obstruction to pulmonary blood flow, Burke and his collaborators [28] noted that in 43 of the 48 cases significant stenosis existed in the infundibulum, either as the only site of obstruction to pulmonary blood flow or coupled with obstruction at the pulmonary valve itself. They conclude that, in many if not most cases, if a direct attack on the barrier to pulmonary blood flow is to be made the attack must involve altering the infundibulum itself. A report by Russell and his co-workers [29] of a woman with normal full term spontaneous delivery following the Blalock operation for tetralogy of Fallot demonstrates that the heart in these cases can sustain not only the burden of the operatively acquired arteriovenous shunt but that of a physiologically acquired placental shunt as well. Both Taussig and Longmire are cited as knowing of other similar patients successfully undergoing pregnancy following this operation.

Retrograde arteriography by means of iodopyracet injected through the left common carotid artery has been shown by Freeman and his co-workers [30] to be of use in assessing preoperatively the exact location, extent and degree of stenosis in cases of coarctation of the aorta previously diagnosed on clinical grounds. A case has been reported [31] of combination of coarctation of the aorta and pulmonary tuberculosis in which left artificial pneumothorax had been introduced therapeutically. Incidental to thorocoscopy, the arch of the aorta and the site of coarctation could be visualized directly and located as a short constriction well below the origin of the left subclavian artery. Although giving information more directly than the x-ray, this procedure is potentially hazardous owing to possible hemorrhage from anastomotic vessels in the chest wall. In reporting a series of 100 patients with coarctation of the aorta on whom he has operated, Gross [32] points out, in accordance with the study by Reifenstein, Levine, and himself, that without surgery only about one fourth of the patients with this condition would live a reasonable life span, averaging at death about 47 years. The remainder die of coarctation or one of its complications at an average age of about 30 years. These deaths are almost evenly

divided between subacute endocarditis or aortitis, sudden rupture of the aorta, and congestive failure or intracranial hemorrhage secondary to the hypertensive state. Of the 100 patients brought to surgery, 9 had thoracotomy only and 11 succumbed from various causes; of these deaths, however, 7 subsequently could be regarded as having been avoidable because of improvements in operative technique or in better preoperative selection of cases. Currently a surgical mortality rate of about 5% can be expected. Of the 80 patients who survived operation, one had no relief of hypertension, 8 had fair relief, and 71 had complete disappearance of hypertension. In view of the over-all figures contained in this paper it seems wise to consider surgery in all cases of coarctation of the aorta discovered at an early enough age to permit a reasonable chance of operative success. Surgical intervention becomes increasingly difficult as premature arteriosclerosis complicates vessel handling in the older patients. Nevertheless, Sokolov [33] reports the successful correction of coarctation in a man of 40 and alludes to another successful correction in a man of 41, performed by Blalock. Clagett and Jampolis,[34] recording their experience with 70 cases in which surgical exploration was performed, the oldest being a person of 50, concluded that an attempt should be made to correct the defect by surgical means regardless of age, myocardial conduction defect, previous cerebrovascular accident, or previous congestive failure.

Gross [35] has further reported the first instance of successful closure of an aortic septal defect, with a three-year follow-up at which time the child seemed entirely normal and no murmur was audible. A surgical attack on complete transposition of the pulmonary veins to the right auricle has been evolved by Muller.[36] Passage of a cardiac catheter into the right lung field from either the superior vena cava or the right auricle was considered evidence of the presence of the transposition. At operation the left auricular appendage was anastomosed to a large superior pulmonary vein. One patient died soon after operation, but the other survived uneventfully and demonstrated an increased exercise tolerance together with disappearance of cyanosis.

II. RHEUMATIC FEVER

The great expectations of a vast and perhaps definitive increase in our knowledge of rheumatic fever and allied diseases aroused by the early reports on the use of adrenal and pituitary hormones have not as yet been fulfilled. The basic nature of the underlying mechanisms in rheumatic fever remains quite obscure, and there is still no single laboratory test diagnostic of this condition. The interplay of possibly significant factors is so intricate and the laboratory data accumulated thereon are already so extensive that no adequate distillation of the pertinent findings can be provided here. The interested reader is referred to the reviews of Swift [37] and Fischel [38] and the more recent splendid condensation by Ehrich [39] of knowledge on the nature of collagen diseases. In fine, Ehrich concludes that collagen diseases are etiologically heterogenous, but postulates that "the common denominator of the various collagen diseases lies in their pathogenesis or, more precisely, in the production by these diseases of abnormal gamma globulins apparently by plasma cells causing injury of the general mesenchyme." Stetson [40] remarks on a consistent correlation between vascular damage to small coronary arteries owing to the presence of microthrombi of leucocytes and platelets and the accompanying presence of typical Aschoff bodies in the hearts of children dying during the course of rheumatic fever. Since he had previously shown that leucocyte-platelet thrombi are associated

with the development of extensive tissue damage during the course of the Arthus and Schwartzman phenomena, Stetson suggests that the concept that these thrombi are of significance in the pathogenesis of rheumatic carditis may form a useful working hypothesis for further investigation. A note of confusion, however, is struck by Valdés-Dapena,[41] who in examining the hearts of 63 tuberculous patients found, in 7, granulomatous lesions in the myocardium which were identical with Aschoff bodies. There were no gross anatomical signs of latent, healed, or active rheumatic heart disease in any of these patients, supporting the view that rheumatic nodules are allergic phenomena due to various allergens rather than the specific response to a specific agent.

Rheumatic fever in the first five years of life has been found by Logue and Hurst [42] to be more common than is generally supposed. Difficulty in recognition has arisen not only from the long-established and erroneous belief that rheumatic fever is rare to absent in this age group and from the tendency to ascribe all murmurs in the very young to congenital heart disease but is also due to its resemblance to endocardial fibrosis. Citing experience in 26 patients with rheumatic fever below the age of 6, the authors observed most frequently fever, apical systolic murmurs, and subjective joint symptoms; elevated sedimentation rate, cardiac enlargement, and apical diastolic murmurs occurred in over one half of the children. The absence of murmurs in a child with congestive failure in the first six months of life suggests endocardial fibrosis. Survival for more than a year and the presence of pericarditis, aortic insufficiency, or very rapid sedimentation rate favor the diagnosis of rheumatic fever.

In the clinical sphere, Freud and his associates [43] report that in 11 rheumatic fever patients who were vaccinated for smallpox 4 cases of definite reactivation of rheumatic fever occurred and in two others there was probably reactivation. The symptoms of reactivation appeared on the first or second day after the take. Whether such reactivation is an allergic manifestation or the result of secondary infection at the vaccination site is not known. The authors suggest that rheumatic fever patients should be vaccinated only when they are directly exposed to smallpox (we believe this to be an extreme view). Brown and his co-workers [44] present the hypothesis that pleuropneumonia or L organisms are antigenic and may produce tissue hypersensitivity and the changes of rheumatic diseases. The use of the presence of C-reactive protein in the blood as a measure of the activity of the rheumatic process in the acute stages is described by Anderson and McCarty.[45] Although the C-reactive protein may be found in a number of different types of infections and hence is by no means specific for rheumatic fever, the authors believe that the presence of C-reactive protein is probably the most sensitive test for the presence of rheumatic activity that we now possess. The role of emotion in rheumatic fever is stressed by Kantor,[46] who considers that rheumatic disease attacks an emotionally sick person in whom psychological tension has lowered the resistance of the host to the invading factor. The author raises the question as to whether the severe personality difficulties of some rheumatic fever patients may be an early choreiform expression and thinks that perhaps all rheumatic children might have chorea if their threshold to its clinical expression were lowered by psychological tension. Security and happiness and, where these are lacking, whatever practical psychotherapy may be brought to bear seem essential to both the treatment and the prophylaxis of rheumatic fever.

Of first importance in the prophylaxis of rheumatic fever is the control and prevention of hemolytic Streptococcus infections, which are generally agreed to be precursors of the disease. In a careful study on the effect of penicillin and chlortetracycline (Aureomycin) on the natural course of streptococcal tonsillitis and pharyngitis, Rammelkamp and his associates ‡ found that chlortetracycline was somewhat more effective in lowering the fever and causing rapid subsidence of symptoms but that penicillin eliminated the carrier state as well; chlortetracycline apparently inhibited the growth of organisms during the period of treatment but had little or no effect on the carrier state. Both antibiotics were equally efficacious in inhibiting antibody formation, and it may be that this feature of their function is as effective in warding off subsequent rheumatic fever as is the rapid cure of the streptococcal infection itself. Unfortunately the effectiveness of this method of prophylaxis is greatly hobbled by the fact that about half of all the persons afflicted with streptococcal infections fail to develop sufficient clinical symptoms to require medical attention. In eradicating the Streptococcus and inhibiting the formation of antistreptolysins three injections of penicillin over a 96-hour period totaling 1,200,000 units gave better results than either a single injection of 600,000 units or two injections of 300,000 units each given 72 hours apart. Massell and his coworkers § found that rheumatic fever recurrences in rheumatic subjects developed after only 2 out of a total of 34 hemolytic streptococcic infections in which penicillin therapy was begun promptly and continued for 10 days. In contrast, there were 6 instances of rheumatic fever following 12 similar infections in which penicillin was not used. Although these observations point to the effectiveness of antibiotic prophylaxis even in known rheumatic subjects, the authors stress that prompt penicillin therapy of streptococcic infections is not recommended as a substitute for the use of continuous prophylactic measures in persons who have had one or more attacks of rheumatic fever. The prophylactic regimen of orally administered penicillin presently recommended is 100,000 to 200,000 units three times daily, at least one-half hour before or two to three hours after meals. To date there has been no report of the development in vivo of penicillin-resistant Group A hemolytic streptococci. The application of these principles to a community program for rheumatic fever prevention has been described by Smith and others.[52]

In a clinicopathologic study of 300 autopsied cases of rheumatic heart disease, Lenel, Strauss, and Schlichter [53] concluded that myocardial lesions and not valvular deformities play the predominant role in rheumatic heart disease. In support of this thesis the authors noted that (1) acute myocarditis was the cause of failure and death in all cases of acute rheumatic fever, (2) the heart failure common in association with subacute bacterial endocarditis was nearly always accompanied by acute myocarditis seemingly secondary to small infarcts, (3) heart failure and death during pregnancy were usually associated with acute rheumatic carditis, while women with severe valvular deformities frequently had uncomplicated pregnancies, (4) a goodly percentage of patients over 50 years of age had severe valvular deformities without cardiac symptoms during life, and (5) extensive fibrosis of the myocardium was a more constant finding than severe valvular deformities in patients developing chronic heart failure.

‡ References 47, 48, and 49.

§ References 50 and 51.

Phenylephrine, a sympathomimetic drug with an arterenol- (noradrenaline-) like action, has aided Besterman [54] in the auscultation of early rheumatic diastolic murmurs. Transient elevation of blood pressure and reflex bradycardia occurred in like degree in both nonrheumatic and rheumatic patients with and without carditis. Phenylephrine induced transient aortic and mitral diastolic murmurs only in a number of the patients with carditis. The aortic diastolic murmurs were attributed chiefly to an increased work load from the hypertension straining a damaged aortic valve; mitral diastolic murmurs were attributed chiefly to an increased mitral flow associated with augmented stroke volume secondary to reflex bradycardia. A strong presystolic venous impulse easily felt over the jugular vein has been described by Vesell [55] as a simple sign characteristic of tricuspid stenosis. On the other hand, Grishman and his collaborators [56] have described 14 cases in which resistance to right atrial outflow with reflux to the liver caused by heart failure, right ventricular hypertension, pericardial effusion, pulmonary hypertension, and interatrial or aortic-atrial shunts resulted in presystolic liver pulsation in the absence of tricuspid stenosis or any organic disease of the tricuspid valve. Levine and others [57] have described two cases in which a clinical diagnosis of chronic rheumatic heart disease was made on the basis of aortic diastolic murmurs but in which at autopsy chronic dissecting aneurysm of the aorta was proved to have occurred in both patients. Both instances were in relatively young persons, were not accompanied during the major part of the illness by the typical chest pain of dissecting aortic aneurysm, and were complicated by congestive heart failure. In neither case was hypertension present.

Despite the great efforts expended in many quarters in the investigation of the role of adrenal and pituitary adrenocorticotropic hormones in rheumatic fever, the major problems remain as yet unsolved. In a series of detailed experiments on rats, Bennett, Berthrong, and Rich [58] have concluded that there is good evidence that both corticotropin (ACTH) and cortisone exert an inhibitory effect upon the development of cardiovascular lesions of hypersensitivity. Spain and Roth,[59] on the other hand, looking for an effect of cortisone and corticotropin on the histopathology of an autopsied case of rheumatic carditis treated with both these agents, found the characteristic lesions of rheumatic carditis present and in no way differing from the changes usually seen in patients not receiving cortisone. It should be noted, however, that death cut treatment short in this case. Adams and his group [60] observed that during corticotropin treatment in acute rheumatic fever the nonspecific hyaluronidase inhibitor level was reduced to normal, paralleling the subjective improvement of the patient. The serum mucoprotein level did not return to normal until approximately three or four months of corticotropin therapy. Whenever corticotropin was stopped or the dosage reduced prior to this drop in mucoprotein levels, the disease recurred. The most coherent explanation of the mode of action of cortisone and corticotropin is provided by Ehrich,[39] who writes:

> The alleviating action of ACTH and cortisone may be "pharmacological" in part. However, in sufficient doses cortisone destroys plasma cells and other lymphoid cells and thus suppresses antibody formation. It enhances protein catabolism and thus causes a more rapid degradation of antibodies and other noxious proteins. It suppresses the permeability of connective tissue membranes and thus interferes with the exchange of components between blood and tissues. It is closely associated with the ascorbic acid metabolism and thus with the formation and

maintenance of connective tissue. It also interferes with the proliferation of fibroblasts and the production of collagen fibers. Observations like these suggest that cortisone is effective through action upon the pathogenesis of the collagen diseases.

On the clinical side, Wilson and Helper [61] found in 11 consecutive patients with acute rheumatic carditis treated with corticotropin every six or eight hours for a period of four to seven days that in every patient clinical evidence was obtained of termination of symptoms and signs of progressive acute carditis during therapy and that the patients were ambulatory two to four weeks from the onset of therapy. Other observers || have been less optimistic, however, and most authorities are in agreement that these hormonal agents simply suppress symptoms of activity and that a given attack of rheumatic fever, despite such suppression, continues on to spontaneous termination in the same period of time that the disease would have run without hormonal treatment. It is not presently known whether cortisone or corticotropin prevents or even significantly diminishes damage to cardiac structures during active disease, and it is clear that the morphologic changes of long standing rheumatic heart disease such as valvular deformities and cardiac hypertrophy are not influenced by hormonal therapy. Nevertheless, as Barnes [65] suggests, the course of treatment should be so planned as to maintain suppression of the acute manifestations of rheumatic fever until the disease has reached the end of its natural duration. The principal value of these hormones to date, as Hench [66] points out, has been their demonstration of the potential reversibility of many diseases hitherto considered to be more or less relentlessly progressive and their manifold applications as powerful investigative tools.

The widespread use of the adrenal hormonal agents has overshadowed but not put an end to interest in other means of alleviating the rheumatic state. Brewer [67] reports that injections of progesterone and estradiol benzoate at four- to eight-day intervals in doses comparable to the amounts of these hormones excreted during the late stages of pregnancy led to satisfactory disappearance of all signs of rheumatic activity in 49 out of 64 patients with rheumatic fever, ranging in age from 3 to 39 years. On oral doses of 4 gm. daily of ascorbic acid, seven patients with acute rheumatic fever showed prompt subsidence of temperature to normal and disappearance of signs of myocarditis and pericarditis in a matter of days, according to Massell and his co-workers.[68] Schaefer and others [69] found that sodium gentisate in doses of 2 gm. orally every three hours controlled the clinical manifestations of rheumatic fever as promptly and effectively as salicylates. In contrast, however, the studies of Rosenberg and his collaborators [70] showed no improvement in objective signs in cases of rheumatic fever treated with sodium gentisate, and these authors concluded that the compound is not an adequately effective therapeutic agent. Using special oxygen chambers for an average of 90 days per patient, Taran and Szilagyi [71] found that 58 children out of 121 with acute rheumatic carditis responded well to oxygen and showed marked clinical improvement. The mechanism of this beneficial action of oxygen has not been determined. Intravenous injection of heparin,[72] *p*-aminobenzoic acid,[73] 3-hydroxy-2-phenylcinchoninic acid,[74] and ultraviolet blood irradiation therapy [75] have all been reported to be of benefit in acute rheumatic fever. Finally, Taran and Jablon [76] accomplished desensitization to the "M" fraction of all known types of hemolytic streptococci in a significant number of rheumatic patients

|| References 62, 63, and 64.

by a slow process of "immunization." It is the authors' feeling that this type of "immunization" seems to have affected the general incidence of recurrences and reactivations in the colony of rheumatic children under observation.

The success of the surgical attack on rheumatic valvular disease is attested by the flood of articles appearing on this subject, and again reference may be made to the Lederle Bulletin [17] for a practical survey of the field. For mitral stenosis, earlier shunting procedures ¶ and valvuloplasty have largely been supplanted by mitral commissurotomy. Results in the first 214 cases of this operation performed by Bailey and his associates [79] were excellent in 89, improved in 70, unimproved in 29, and death from various causes in 26. In percentages, the operative mortality was approximately 10%, and improvement 75%. In selecting cases for surgery, these authors believe strongly that the best group for surgical intervention comprises those in whom the symptoms of mitral stenosis are just becoming noticeable but are not actively progressive. By operating thus early in the course of the disease they seek to prevent steady worsening and in particular to avoid irreversible pulmonary vascular changes secondary to pulmonary artery hypertension. A considerably more conservative position on the indications for surgery for mitral stenosis is taken by Bland,[80] on the basis of a careful 20-year follow-up of 1,000 cases of childhood rheumatic fever.[81] The group as a whole did surprisingly well, with 699 of the patients alive at the end of 20 years, at an average age of 28. Furthermore, three out of four of these survivors had little or no limitation. A pure form of mitral stenosis developed in 117 of the group, but in only 12 had serious pulmonary hypertension appeared, as evidenced by acute pulmonary edema. Since even the pure form of mitral stenosis does not always represent a high degree of narrowing of the orifice and relatively slight degrees accompanied by little or no cardiac enlargement may be well borne for years without serious difficulty or apparent progression, Bland considers too drastic the proposal that early commissurotomy under these circumstances might prevent the later development of higher degrees of obstruction and thereby protect the lungs. There is risk, indeed, that appearance of significant mitral regurgitation secondary to mitral commissurotomy might actually promote the damage to the pulmonary tree that it is designed to prevent.[82] Hence for the time being the considerable hazard of surgery might better be reserved for those more immediately in need of relief. Harken and his associates [83] concur in this general evaluation, considering progression of symptoms the urgent indication for surgery. The terminal state, although increasing the surgical risk, justifies a trial of surgery despite possible irreversible changes in lung, liver, and myocardium, because under medical management alone the disease is about as malignant as cancer. In the large group of those who are merely handicapped, in whom the disease is nonprogressive, however, surgical intervention might well be withheld awaiting further developments in techniques of cardiac surgery, unless the patient is clamorous for present relief. Another good discussion of selection of patients with mitral stenosis for surgical treatment is given by Andrus.[84] Wilcox and Grace [85] particularly emphasize that any left atrial enlargement associated with mitral stenosis will almost assuredly also be associated with some degree of mitral regurgitation, and they go so far as to say that no grossly enlarged heart in mitral stenosis should be operated upon, because mitral valvulotomy, even in the best hands, is likely to be accompanied by some

¶ References 77 and 78.

additional degree of regurgitation (this is a point of view which we do not fully share). As Murray [86] points out, it is not known as yet how long the beneficial results from mitral valvulotomy will last nor whether the rheumatic disease will reactivate and heal up the incision made in the valve. With this point in view, it is of interest to note Magarey's [87] belief (first expressed years ago by Rokitansky) that there is ample evidence to show that progressive postrheumatic valvular thickening and the development of mitral stenosis are due in part at least to the organization of repeated deposits of fibrin on the surface of the valves, and in the commisures between the cusps, and that it is not necessarily dependent upon the accepted process of postinflammatory cicatricial contraction within the substance of the valve. Magarey consequently feels that surgical intervention by cutting the commisures may still predispose to repeated fibrin thrombus formation and so to recurrence of stenosis. In general, the results of commissurotomy to date have been extraordinarily successful but further advances in the surgery of rheumatic valvular disease, as in congenital heart disease, await the development of techniques permitting a direct approach to the valve sites in a bloodless field.

Prophylaxis against embolization in rheumatic heart disease was attempted by Madden [88] and by Baronofsky and Skinner [89] in a few cases wherein they ligated and resected the left auricular appendage. More recently, Leonard and Cogan [90] have reported a failure following this operation, a recurrent embolus occurring in one of their patients on the ninth postoperative day. That failures are to be expected with this type of surgery is evident from the reports of Jordan, Scheifley, and Edwards [91] and Daley and his collaborators,[92] who showed in extensive autopsy studies that in only one half or fewer of cases were mural thrombi limited to the left auricular appendage. The good results reported by Cosgriff [93] and by Askey and Cherry [94] support the belief that at present the best prophylaxis against recurrent embolization is indefinitely prolonged ambulatory anticoagulant therapy.

III. BACTERIAL ENDOCARDITIS

The highly successful offensive against bacterial endocarditis which began a decade ago with the introduction of penicillin has arrived at a seemingly irreducible minimum of unavoidable fatalities, and the advances of the last three years have largely been in the nature of straightening the line. Interest in the syndrome nonetheless continues active, and much interesting information and speculation have accumulated. The experimental production of endocardial vegetations as a result of an increased work load on the heart has been reported by Lillehei and his co-workers.[95] By creating large arteriovenous fistulas in dogs and thereby lowering the peripheral resistance, the authors induced a sixfold increase in cardiac output. At autopsy 3 to 10 months later dogs with large fistulas invariably showed adrenal glands two times larger than normal, and in these animals there was usually found well-developed endocarditis, with vegetations on both the mural and valvular surfaces. These varied from soft friable vegetations similar to those seen in human bacterial endocarditis to firm smooth vegetations typical of rheumatic endocarditis. Micro-organisms were usually found in the blood. Dogs killed sooner after the establishment of the fistulas usually showed enlarged adrenal glands without endocarditis, suggesting that adrenal hypertrophy precedes the development of the heart lesions.

In a detailed study of the myocardiums in 76 fatal cases of endocarditis, Saphir, Katz, and Gore [96] demonstrated in every instance the presence of at least one of the five principal varieties of histological alterations observed in this series. These changes included direct extension of the suppurative process into the adjacent heart muscle, ischemic changes secondary to coronary embolization or localized endarteritis, toxic changes similar to those in diphtheria or in myocarditis of various infectious etiologies, changes secondary to bacterial seeding and the resultant inflammatory reaction, and, finally, although in less than 10% of the cases, Aschoff bodies residual from the predisposing rheumatic heart disease. Similar observations were made by Perry and his associates [97] on 52 cases. Neither group of observers could distinguish any difference between the lesions in patients treated with penicillin and those in the untreated groups, probably owing to the death of the treated patients prior to the elapse of sufficient time for complete repair of the myocardial lesions.

The significance of these myocardial lesions is apparent when one recalls that the principal cause of death in currently reported series of bacterial endocarditis is congestive heart failure, occurring despite bacteriological cure. As emphasized by Correll and his associates,[98] although occasionally this heart failure results from excessive valvular destruction, usually it follows the development of myocarditis permitted by delay in diagnosis and treatment.

The advent of successive antibiotics has served perhaps more to complicate than to facilitate the treatment of bacterial endocarditis, and penicillin alone or in combination with other antibiotics or "blocking" agents remains the drug of choice in the majority of instances. The nub of the problem, according to Hunter,# lies in the fact that even with the help of bacteriostatic agents which suppress bacterial multiplication with great efficiency body immune responses are inadequate to overcome endocardial infection. Despite numerous recorded successes, chlortetracycline, chloramphenicol, and oxytetracycline (Terramycin) must on the whole be classed with sulfadiazine as primarily bacteriostatic in this disease. What is needed is a bactericidal agent, and in this regard penicillin and to a lesser extent streptomycin remain preeminent. Some insight into the reason for this superiority is offered by the work of Nathanson and Liebhold,[101] who showed that penicillin and streptomycin penetrate and possess antibacterial activity in fibrin, while sulfonamides do not. These observations support the concept of a fibrin barrier on the valve acting to protect the organism from harmful agents and emphasize the likelihood that an essential property of any therapeutic agent for bacterial endocarditis must be its ability to penetrate and show antibacterial activity in fibrin. Incidentally, these observations provide further justification for the omission of heparin from the therapy of endocarditis, since fibrin does not appear to prevent the action of penicillin and streptomycin. In vitro studies by Hunter [102] of clots infected with enterococci and exposed to high concentrations of chlortetracycline in the surrounding medium for prolonged periods still showed a high count of viable organisms, and even with penicillin-sensitive strains of viridans Streptococcus chlortetracycline and oxytetracycline generally had only a bacteriostatic effect. Hamburger and Stein [103] have explored the possibility of truly massive penicillin dosages in the treatment of patients with endocarditis caused by penicillin-sensitive streptococci, and their findings are potentially of great significance. These workers, in a series of 12 patients,

References 99 and 100.

administered crystalline sodium penicillin G at the rate of 16,000,000 units every three hours, intramuscularly, and continued this treatment for two weeks. Ten of the 12 patients were still living from 8½ to 47 months after the course of treatment, although two had had relapses within a month after treatment for which a second two-week course was curative. The remaining two patients died of cardiac failure and pulmonary infarction, respectively, but at postmortem examination careful studies indicated that bacteriological cure had been effected. The economic advantages of forestalling the additional two to six weeks of hospitalization which might be consumed in current methods of treatment of this disease are obvious, but the authors stress that the method is still in the experimental stage and is applicable solely to definitely penicillin-sensitive streptococci. Bacteriological cures were not obtained in two cases caused by Streptococcus fæcalis, for which the minimal inhibiting concentration of penicillin was 6.25 units. In this connection mention may be made of the work of Eagle and his collaborators [104] on the effect of schedule of administration on the therapeutic efficacy of penicillin. These authors demonstrated that the aggregate time that penicillin remains at effectively bactericidal levels is more important than the absolute concentration, provided only that the latter is in excess of the level which in vitro kills the particular organism at the maximum rate. Large doses of penicillin are more effective than smaller doses primarily because of the longer time during which they provide that effective concentration. Further studies are in order as to the reliability of the short-term massive dosage regimen, but in view of Hunter's comments alluded to above on the need for a constantly bactericidal program in the treatment of endocarditis, it may yet prove the most efficient, economical, and life-saving. A case in point is that of Whipple,[105] who cured a patient with a very resistant viridans Streptococcus endocarditis with average daily doses of 86,000,000 units of penicillin for one month.

The necessity of controlling its use with frequent blood level determinations, together with relative cheapness of penicillin at the present time, have combined to reduce the expected clinical usefulness of carinamide as an agent capable of enhancing the blood levels of any given dose of penicillin from two to seven times. Since it may still be of value in some cases, it is noteworthy that Boger and Crosson,[106] in studying 1,997 patients to whom the drug was administered, demonstrated that, exclusive of nausea in 12% and vomiting in 5.5%, the incidence of toxic manifestations and true drug sensitivity was less than 2%. There was no evidence that carinamide interfered with the excretion of normal nitrogenous metabolites nor permanently impaired renal functions. The authors noted three patients in the series who were on adequate doses of digitalis prior to the introduction of carinamide, and in these yellow vision and other clinical and electrocardiographic evidences of digitalis intoxication developed rather promptly; these disappeared with withdrawal of the carinamide and without change in the digitalis dose. Probenecid (Benemid), a new compound, *p*-(dipropylsulfamyl) benzoic acid, has been shown by Boger and his group [107] to possess similar properties in lower doses to carinamide.

One of the most respected of the infecting organisms in subacute endocarditis, the Enterococcus (Streptococcus fæcalis), is unique amoung nonhemolytic streptococci in its pronounced tendency to produce pyogenic and encapsulated lesions. According to Loewe, Candel, and Eiber,[108] the invasive property of this bacterium is further evidenced by the fact that it may attack normal heart valves, thus giving rise

to cases of endocarditis not accompanied by history of preceding heart disease. Suppuration of the myocardium and other viscera is fairly common and Enterococcus myocarditis is of almost uniform occurrence. On the credit side, however, the ulcerative undermined type of endocarditic lesions observed with Enterococcus infections minimizes friable thrombus formation and hence reduces markedly the incidence of renal, splenic, and cerebral embolizations. The authors stress heavily the necessity for early treatment, before mycotic aneurysms and pyogenic lesions of the myocardium and other organs occur. Once they are established, no amount of intensive therapy is sufficient to sterilize these metastatic encapsulated purulent lesions, which serve as seeding foci for reinfection. The authors propose that this type of endocarditis be treated at the outset with at least 10,000,000 units a day of penicillin for at least five weeks, longer if the patient has deteriorated or if previous treatment has proved inadequate. If there is any indication from the patient's course that improvement is not occurring, streptomycin is added at the rate of 2 gm. a day. There appears to be general agreement * on this program, although most observers start treatment with both agents simultaneously. As noted by Hunter, the high risk of damage to the vestibular apparatus by the streptomycin is more than outweighed by the potentially fatal nature of the illness if it is not cured. Nesvadba emphasizes that the two antibiotics may effect a cure despite the fact that complete resistance of the micro-organism to both may be found in vitro.

It must not be supposed from the foregoing paragraphs that the newer antibiotics have no role in the treatment of endocarditis. Levinson and his collaborators [112] found chlortetracycline effective in two instances of penicillin-resistent Staphylococcus endocarditis. Rubenstein and Austin [113] used chlortetracycline and oxytetracycline in combination to cure an enterococcal endocarditis, after failure of triple antibiotic treatment with penicillin, streptomycin, and chlortetracycline. In this instance the authors felt that the response was principally due to the oxytetracycline. There have been scattered successes † with chloramphenicol against various organisms including a case of Actinomyces muris endocarditis reported by Stokes and his group.[116] A potential troublesome complication of any prolonged administration of the antibiotics which sterilize the intestinal tract is exemplified by the case of Gewin and Friou,[117] wherein cure of a penicillin-resistant Staphylococcus endocarditis occurred with combined use of chlortetracycline and chloramphenicol. During the course of treatment, however, many severe side reactions developed, including mucosal changes in the mouth and gastrointestinal tract, skin lesions, and peripheral neuritis suggestive of avitaminosis B, as well as a complicating fungus infection of the skin. Vitamin administration was only partially effective in controlling these manifestations until the antibiotics were discontinued. Despite these and similar successes, however, careful observers, including Friedberg,[118] and Kane and Finn,[119] feel that chlortetracycline should be regarded only as an adjunct to penicillin in the treatment of bacterial endocarditis, largely because the action of chlortetracycline in the doses given and tolerable by the average patient is bacteriostatic and not bactericidal. Chlortetracycline is indicated in the treatment of endocarditis in which the causative organism, either streptococcal or other, is penicillin-resistant; in endocarditis due to Gram-negative organisms sensitive to chlortetracycline, and in com-

* References 109, 110, and 111.

† References 114 and 115.

bination with other antibiotics in instances in which sensitivity determinations in vitro suggest that such combination may be effective. Marked allergic sensitivity to penicillin on the part of the patient constitutes another indication, as pointed out by Geraci,[120] working with oxytetracycline. According to this author, there is some in vitro evidence indicating that early and rapid development of a high degree of resistance to the streptomycin used in the treatment of streptomycin-sensitive Gram-negative organisms can be prevented when oxytetracycline is given together with the streptomycin. This provides an additional indication for the use of oxytetracycline.

Some mention must be made, despite the complexity of the subject, to antibiotic antagonism and synergism. Interference by chloramphenicol with the rate of bactericidal action of penicillin in in vitro studies on enterococci was first noted by Jawetz and his associates,[121] in 1950, and was subsequently shown to be present in in vivo studies on mice, using chloramphenicol, chlortetracycline, or oxytetracycline. The degree of interference with the therapeutic action of penicillin varies with the drug and the dose and is greatest when relatively ineffective doses of the newer antibiotics are added to doses of penicillin which, if given alone, would cure 70% or more of the animals. The antagonism becomes less as the dose of "interfering drug" increases to the point of being curative by itself. Hunter [102] suggests, as a possible explanation, that penicillin has been shown to kill only those organisms which are in the process of active multiplication; when another antibiotic is present which inhibits multiplication but fails to kill then organisms no longer are killed by penicillin. It is not clear whether this phenomenon of antibiotic interference is of clinical significance, and some animal experiments by Ahern and his colleagues [122] suggest that this may not be the case. These workers confirmed the interference of chloramphenicol with the early bactericidal action of penicillin but subsequently demonstrated that that interference is not a factor when effective antibiotic blood levels are maintained for two or three days. Antibiotic synergism is best illustrated in the field of endocarditis by the effectiveness of penicillin and streptomycin against the Enterococcus, as already described above. Penicillin alone, even in large doses, is often ineffective, yet when accompanied by concentrations of streptomycin which alone have no demonstrable effect the two agents can lead to cure in many instances. Synergistic action of several combinations of antibiotics have been reported in a number of cases, but the efficacy of such combinations must be tested anew and empirically against the organism obtained in each new case of endocarditis, creating thereby a laboratory problem of recurrent and formidable character. Hunter suggests the possible extension of the synergistic action of streptomycin to the massive penicillin two-week treatment of penicillin-sensitive streptococcal endocardial infections discussed previously, providing that further experience with this program establishes its value. The hazard of eighth nerve damage is again offset by the enhancement of the patient's prospect of a rapid cure and early release from hospitalization.

In addition to the case of Actinomyces muris endocarditis reported by Stokes, Wolfe and Henderson [123] have reported a case in a diabetic of endocarditis due to Candida krusei, and Fawell and his co-workers [124] have noted an instance in which Histoplasma capsulatum was the infecting organism. Although the latter two patients failed to respond to treatment, and, indeed, in the second case the diagnosis of subacute endocarditis was discarded because of persistently negative blood cul-

tures and the lack of response to antibiotic therapy, the authors urge that mycotic endocarditis be considered a possibility in any obscure febrile illness with negative cultures and a poor therapeutic response.

Acute endocarditis remains a medical emergency with high fatality rate and frequent refractoriness to treatment despite the multiplicity of antibiotic agents available. A possible explanation for the high proportion of treatment failures in the acute disease is provided by Sheldon and Golden,[125] who demonstrated single or multiple abscesses of the valve rings in the hearts of 12 patients with acute bacterial endocarditis who had received penicillin therapy. The abscesses measured from one to several centimeters in size, often involved more than one valve ring, and in many cases ruptured either into the heart chambers or the sinuses of Valsalva. In these cases the valve ring abscesses were the only recognizable foci of persistent acute inflammation, the actual endocarditis and its embolic and associated infectious manifestations generally showing advanced healing. On the basis of experience with four recent cases, Applebaum and his associates [126] stress the necessity of keeping an early and close watch for the onset of acute endocarditis as a complication of bacterial pneumonia. They emphasize as essential criteria for the diagnosis of this complication the development of murmurs, particularly in diastole; evidence of impaired myocardial function; changes in the size and contour of the heart on x-ray; the presence of embolic phenomena, and the persistence or recurrence of fever and positive blood cultures despite improvement in the primary disease. All of their patients died, and in each one a rapidly progressive aortic regurgitation secondary to ulceration or perforation of the aortic valve occurred and led to the development of a severe degree of heart failure. At the first suggestion of this complication, intensive antibiotic treatment must be started and maintained for a relatively long period, perhaps a minimum of six weeks. Of especial interest, because of the continuing deadliness of acute staphylococcic endocarditis, is the report of Friedberg and Bader [127] of the first case of this infection in which cure followed the parenteral use of bacitracin. Huge doses of penicillin, chlortetracycline, and chloramphenicol over a 12-day period had previously failed to control the disease. The fever fell promptly after the addition of bacitracin, and the patient remained afebrile thereafter. There were no significant renal nor other toxic manifestations as a consequence of the bacitracin administration. In view of the high incidence of penicillin-resistance in Staphylococcus aureus endocarditis, the demonstrated clinical effectiveness and tolerability of this antibiotic are most welcome.

Finally, practical criteria for the prophylaxis of subacute bacterial endocarditis have been summarized by Ernstene and his co-workers.[128] They recommend that all patients with congenital or valvular heart disease be given penicillin procaine (in doses which various authorities suggest be from 400,000 to 1,000,000 or 2,000,000 units) before and for five days after dental extractions, tonsillectomy, spontaneous or therapeutic abortion, and spontaneous or induced labor, and longer if fever is present and during acute upper respiratory infections and in the presence of infected wounds for a minimum of five days, or until all evidence of infection has cleared. For the patient who is doubtful that his life is worth that much trouble, reference can be made to the revelation [129] that in 1948 the estimated cost to private patients for all expenses incidental to treatment for subacute endocarditis, exclusive of physicians' fees (and not necessarily curative), was $601.61.

IV. PERICARDITIS AND MYOCARDITIS

Acute benign nonspecific pericarditis has occasioned considerable interest in the past few years, and the major clinical features, being generally well known,‡ need no repetition here. The etiology remains unknown. In one patient in Evans' series mild pericarditis developed shortly after he visited another patient with the same illness, but there is no other report of possible contact transmission of the disease, and this instance may well have been pure coincidence. Few long-term follow-up studies have been reported in the literature, but to date no clear-cut instance of chronic constrictive pericarditis has resulted among the cases observed. A number of recurrences of the acute phase of the disease have been reported, but in all instances the patients ultimately did well. Taubenhaus and Brams,[135] using chlortetracycline, and Rosenow and Cross,[136] using both chlortetracycline and oxytetracycline, recorded rapid relief of symptoms and decrease in fever and pulse rate promptly after starting therapy. Owing to the variability of the illness, however, more details of this type of treatment will be necessary before the value of these antibiotics is established.

Two cases of rather marked pericardial effusion mistaken for cardiac enlargement in severe anemia have been reported by Soloff and Bello.[137] In a severe case of Cooley's erythroblastic anemia the x-ray finding of "huge cardiac enlargement" was shown at autopsy to result from a normal-sized heart within a massive pericardial effusion. On the basis of this experience, the authors subsequently performed a pericardial tap on a patient with pernicious anemia in relapse, with x-ray showing the heart as being moderately enlarged in all diameters. A repeat x-ray after the removal of 150 cc. of pale amber fluid and replacement of 300 cc. of air demonstrated a relatively normal-sized heart with a bilateral pericardial fluid level. With treatment for the anemia, the effusion slowly disappeared. Angiocardiography has been found useful in differentiating pericardial effusion from cardiac hypertrophy in eight cases reported by Levy and his co-workers.[138] As a bedside maneuver, the finding of a normal or only slightly prolonged arm to tongue circulation time has been used by Bellet and others [139] to differentiate massive pericardial effusion from dilatation of the heart; in the latter circumstance a markedly prolonged circulation time is expected. When pericardial effusion advances to the point of actual cardiac tamponade, Elkin and Campbell [140] have found in a study of 17 patients that conservative management consisting either of supportive measures alone or one or two pericardial aspirations brought good results, with the exception of a single patient who died a short while after aspiration was performed. Surgical intervention should be reserved for patients failing to improve on this program. A good summary of the techniques and hazards of pericardial aspiration has been given by Kotte and McGuire.[141] The occasional surprise diagnostic value of pericardial aspiration has been described by Seaman and Christerson [142] in a case in which acute disseminated lupus erythematosis was first diagnosed from the finding of L. E. cells in the buffy coat smear of the patient's oxalated pericardial fluid. The pericardial effusion in this instance resorbed rapidly under cortisone treatment.

In discussing chronic constrictive pericarditis, Paul [143] draws a distinction between this entity (concretio cordis, Pick's disease) on the one hand and chronic mediastinopericarditis (accretio cordis) on the other. The former condition, believed

‡ References 130, 131, 132, 133, and 134.

usually to be tuberculous in origin, presents a diffusely scarred, thickened, and often calcified pericardium, resulting in total obliteration of the pericardial cavity, splinting of the myocardium, a reduction of cardiac output, and symptoms and signs of chronic venous congestion. In the latter instance the pericardium is firmly attached by scar tissue to multiple surrounding thoracic structures, rigidly fixing the heart in the chest cavity. Although the pericardium may be somewhat thickened and the layers fused together, myocardial splinting and obstruction to circulation does not occur. It is considered to be the late result of rheumatic fever and is associated with valvular heart disease, which chiefly accounts for the unusual myocardial hypertrophy and disability present in these latter cases. Both Paul and McKusick [144] suggest that the reason why a tuberculous etiology of chronic constrictive pericarditis is not demonstrated more often in patients in this country is that most of the patients studied have been further along in their disease, having passed the point where tubercle bacilli or typical tubercle formation could be expected and reached a stage of nonspecific hyalinized and calcified pericardial scar. A case of constrictive endocarditis, a rare entity alluded to by Bland [145] but almost unknown in the American literature, has been described by McKusick and Cochran.[146] The predominant physiologic defect in this patient was impediment to diastolic filling of the ventricle, and the patient's clinical findings so mimicked chronic constrictive pericarditis that thoracotomy was performed, showing an abnormally enlarged and tensely distended right auricle but a normally delicate pericardium without adhesions. At autopsy the endocardial surfaces of both ventricles were markedly thickened by a layer of fibrous tissue which measured up to 4 mm. in greatest thickness.

Pericardiectomy for chronic constrictive pericarditis is well established. Evaluating their own surgical results, Chambliss and his group [147] found 72% improvement among 61 patients operated upon. Adding their own cases to those already in the literature, these authors found that of a total of 415 cases reported in which operation was done satisfactory results had been obtained in 258, or 62%. The cases cited have all been in the late stage of concretio cordis, and there has recently been advocacy of much earlier surgical intervention in tuberculous pericarditis. In a study of 41 cases of clinically primary tuberculosis, Wood [148] has shown that the prognosis may be considered poor in the presence of advanced age (over 50 years), a gradual onset of symptoms, the occurrence of cardiac arrhythmias, and positive proof of tuberculous etiology. No prognostic significance may be given to the presence of a pericardial friction rub, pericardial effusion, or congestive failure. The mortality rate in the first year after the onset of symptoms is approximately 50%. These findings are of interest in view of the report of Holman and Willett [149] of the treatment of five active cases of tuberculous pericarditis by pericardiectomy. Conceding that streptomycin and other antibiotics are of primary importance in modifying previous conceptions as to the treatment of this condition, these workers reached conclusions quite at variance with those of previous authorities who felt that the results of surgery performed during the period of tuberculous activity were uniformly discouraging. Early pericardiectomy liberates the heart from the mechanical effects of the pericardial effusion and permits a more efficient attack on the inflammatory component. Technically the operation is easier in the stage prior to the solid fusing of the epicardium and the pericardium. Furthermore, early surgery undoubtedly reduces greatly the involvement of the myocardium, which may be far advanced in late cases. Of the five patients operated on at this early stage, tuber-

culosis was demonstrated by positive cultures obtained at the time of operation in four and by the finding of tubercle bacilli in the tissues of the fifth. Notwithstanding, all operative areas healed by first intention, resulting in the cure of three of the patients and progressing improvement in the other two. Herrmann and his associates [150] have also been convinced that pericardiectomy should be considered early in tuberculous pericarditis, immediately after a course of streptomycin and *p*-aminosalicylic acid (PAS) therapy. As Blalock [151] points out, however, a longer period of follow-up is required for accurate assessment of this therapy, since "inflow stasis" occurs fairly frequently in tuberculous pericarditis with effusion, and many cases do not progress subsequently to chronic constrictive pericarditis, thereby occasioning obvious difficulties in the selection of cases for early pericardiectomy. The prompt and persistent improvement of tuberculous pericarditis treated with streptomycin, reported by Natelson,[152] suggests further that a conservative position is justified. Two interesting cases of tularemic pericarditis recorded by Meredith [153] emphasize the difficulty of decision. One required ultimately a pericardiectomy for the relief of constrictive pericarditis, and the other recovered completely on medical management despite pericarditis with effusion and cardiac embarrassment existing for almost one year. A final curiosity is the case of Slater and others [154] of chronic constrictive pericarditis produced by diffuse metastatic carcinoma of the pericardium, the only metastasis from a primary breast carcinoma completely resected 14 years before.

An association of myocarditis with pericarditis is suggested by Godfrey,[155] who noted in three cases of acute nonspecific pericarditis clinical and electrocardiographic evidence of myocardial injury which persisted seven months, one year, and two and one half years, respectively, after the onset of the acute pericarditis. The author concludes that nonspecific pericarditis is not always unequivocally benign and that it may occasionally be followed by prolonged and perhaps permanent myocardial injury. The fact that all three patients were over the age of 50 years and that one of them had known hemachromatosis raises the possibility that other causes may have underlain the observed myocardial changes. Fine, Brainerd, and Sokolow [156] have reported serial clinical and electrocardiographic studies made on 84 patients suffering from a variety of acute infectious diseases, and of this number exactly one third showed electrocardiographic abnormalities as compared with their own normal control records. Most of the latter group showed one or several abnormal clinical signs considered consistent with myocarditis. Except in diphtheria, however, myocarditis as evidenced by these findings did not seem to be decisive in determining the survival of the patients, who generally were unaware of its presence. In a series of autopsies done in cases of fatal poliomyelitis Spain and others [157] found evidence of myocarditis in 12 of 14 patients, yet in only one patient had clinical evidence of myocarditis been found. Weinstein and Shelokov [158] noted that abnormalities of the electrocardiogram occur frequently in the acute phase of poliomyelitis. Mild forms of myocarditis they consider probably to be hypoxic in origin, whereas more severe examples they ascribe to invasion of the myocardium by the virus itself. Sterile verrucous endocarditis may occur in poliomyelitis. The relatively common occurrence of acute pulmonary edema in fatal bulbar poliomyelitis has led the authors to urge strongly the subcutaneous rather than intravenous administration of water and electrolytes to the patient unable to swallow and to emphasize the use of small amounts. Acute onset of fever, cutaneous "rheumatic" manifestations, and transient

changes in the electrocardiogram considered to be characteristic of myocarditis were observed by Neidhart and Rumrich [159] in six young adults in all of whom within 8 to 12 weeks signs of acute tuberculosis developed, one dying of miliary dissemination. The authors believe this to be an allergic tuberculous myocarditis, occurring in primary tuberculous infection of the adult. Rose [160] reports a case with various types of heart block in which at autopsy was demonstrated tuberculous myocarditis with diffuse degeneration of the myocardium and focal caseous tuberculosis. The disease was also present actively in the pelvic organs but not in the lungs.

The term myocardosis has been applied by Lyon [161] to reversible electrocardiographic changes noted with infectious hepatitis; he ascribes the changes to a metabolic disturbance related to a drop in plasma proteins, especially the albumin. A more advanced and irreversible stage of the same process is reported by Oppenheim,[162] who studied 169 cases of cirrhosis of the liver, 78 with autopsy, for the presence of degenerative changes in the myocardium. Myocardial involvement could be demonstrated clinically in most of the living patients and histologically in all of the autopsied ones. Again there was a definite correlation between the degree of hypoproteinemia, the abnormalities in the electrocardiogram, and the prognosis of the patients. The author concluded that this represents a hepatogenic metabolic disease of the heart. The cardiac status of 109 men who had suffered from beri-beri and severe malnutrition during 44 months as Japanese prisoners of war has been evaluated by Griffith.[163] Those surviving and properly treated did not have residual clinical heart disease. Incidentally, it did not appear that the 44 months on low-calorie low-fat diet decreased the incidence of arteriosclerosis in these men.

A good assessment of the cardiac complications of hemochromatosis has been presented by Bothwell and others,[164] who find cardiac hemochromatosis commonly associated with arrhythmias and nonspecific electrocardiographic abnormalities. The average survival period after onset of cardiac symptoms is less than one year. Congestive failure is the usual cause of death, and response to medical treatment is poor. The cause of heart failure in hemochromatosis is not known. The authors conducted radioiron studies in two younger patients and showed that young subjects with hemochromatosis absorb greater quantities of iron from the intestine than do older persons. On the basis of this finding they postulate that the higher incidence of failure in the younger persons with hemochromatosis may be related to the more rapid rate of absorption and deposition of iron in the heart rather than to the total quantity deposited, which may be extreme in older patients showing nevertheless no clinical signs of myocardial damage whatever. Clinical evidence of heart disease was found in 13 of 21 patients with acromegaly by Hejtmancik and his group,[165] who ascribe the cardiac hypertrophy and interstitial fibrous tissue proliferation found in these cases to a direct effect of the anterior pituitary hormone. The hypertension sporadically seen in persons with acromegaly is poorly tolerated by the heart. Six cases of Friedreich's ataxia with associated cardiac manifestations have been recorded by Nadas and others.[166] Postmortem studies in one showed diffuse myocardial fibrosis and extensive coronary artery obstruction, chiefly in the left ventricle; the authors advance the theory that such coronary artery disease may be the etiologic factor in the myocardial injury found in these cases. A reminder that sulfonamide sensitivity may underlie myocardial damage is given by Lilienfeld and his co-workers,[167] who describe a case of acute myocarditis with bundle branch block following the use of sulfadiazine.

An extensive study of atrophy of the heart has been conducted by Hellerstein and Santiago-Stevenson,[168] who found 85 instances in a review of 2,000 consecutive autopsies. Forty-four subjects had excess pigmentation (brown atrophy), and 41 had simple atrophy. Atrophy occurred in conjunction with a variety of diseases, most frequent of which were neoplasms and chronic infection, and the common factors predisposing to general body atrophy and therewith to heart atrophy were considered to be prolonged illness, from 2 months to 17 years; prolonged bedfastness, and malnutrition producing an average of 26% weight loss. There was a definite trend for the blood pressure to fall during the course of an illness during which cardiac atrophy developed. Clinically diagnosed cardiac decompensation, however, occurred in only 3 of the 85 patients, confirming prior observations that the atrophic heart is usually adequate to meet the mode of life. The authors observe that the recovery of experimentally starved animals and man and of inmates of concentration camps indicates the reversibility of atrophy of the heart and body. The decrease of blood pressure and heart weight in the hypertensive patients in this series indicates that hypertrophy may proceed to atrophy under the proper circumstances. It might therefore be desirable in some cases to produce cardiac atrophy by controlled undernutrition in order to reduce cardiac work and reverse or halt a process of hypertrophy. Nine cases of heart disease of unknown etiology have been reviewed by Davis and his collaborators,[169] and the pathological findings and possible etiological factors are discussed. Observing that in rheumatic fever, after recovery from the acute rheumatic myocarditis, fibrosis and hypertrophy are uncommon unless there is resultant valvular deformity, these workers find it difficult to assume that minor illnesses may result in such severe heart disease occurring months to years after an infection in a few persons, yet with the majority of persons suffering from the same disease escaping without cardiac sequelae. Seven of the nine cases occurred in young Negro adults, possibly indicating a racial factor. On the whole, however, the authors believe that attention should be directed to the study of other physiological factors in cardiac muscle hypertrophy, particularly derangements in the metabolism of the heart muscle cell. Lind and Hultquist [170] describe five cases of isolated myocarditis among newborn and infant children, four of whom came to autopsy. Although in two cases the myocarditis was thought to be congenital, the cause of the disease could not be explained in any of the children. Reporting on interstitial myocarditis in children, Tedeschi and Stevenson [171] conclude that the so-called "isolated myocarditis" is in reality a manifestation of a more generalized disease process and that a number of unrelated factors and agents apparently of a mild nature individually may lead under special circumstances or in predisposed persons to severe myocardial complications. A beneficial response of at least six months' duration in a case of familial idiopathic hypertrophy of the heart with congestive failure and ascites treated with corticotropin has been recorded by Bland and Friedlich.[145]

V. CORONARY ARTERY DISEASE

Among the most important and possibly significant studies in cardiovascular disease during the past three years have been those concerned with the pathogenesis of atherosclerosis. The problems are so complex and the contributions so varied that only a few of the most striking developments can be reviewed here. Worthy of note at the onset is the distinction, stressed by Moschcowitz [172] but all too often lost sight of, between ordinary hyperplastic arteriosclerosis and atherosclerosis. There

is good reason to consider the former process purely one of normal aging, the inevitable destiny of all animals that possess a vascular system similar to the human one and who survive their expected term. In other words, normal intravascular pressure and its increased gradient, hypertension, if given sufficient time result in anatomic change. Factors modifying this fundamental mechanism include the composition of the blood, perivascular stresses and fixations, the vascular supply of the blood vessel walls, and doubtless other contributing factors yet to be determined. Although anatomically demonstrable in almost all persons surviving long enough, hyperplastic arteriosclerosis causes disease only when the circulation of a vital organ is impaired. Atherosclerosis, on the other hand, is not a primary lesion, is by no means universal, and is at best only a part or a facultative lesion of arteriosclerosis. In an interesting extension of these thoughts to the association of hyperplastic arteriosclerosis and diabetes mellitus, Moschcowitz[173] concludes that in older persons hyperplastic arteriosclerosis precedes but does not follow the diabetes. The higher incidence of gangrene of the lower extremity as compared to that in nondiabetics, together with vessel changes found in juvenile diabetics, are atherosclerotic in origin rather than arteriosclerotic and are secondary, he believes, to hypercholesteremia.

Detailed pathological and biochemical studies tending to confirm these concepts are lucidly summarized by Thannhauser.[174] In the presence of prolonged hypercholesteremia, as in the familial variety, a demonstrable accumulation of cholesterol in the intimal and subintimal cells may occur. The cushions of cholesterol-laden cells thus accumulated may ultimately regress, may persist for a lifetime without softening or disintegration, or may disintegrate, leading to fibrous tissue invasion and ultimate sclerosis of the arterial wall. In the ordinary type of arteriosclerosis, on the other hand, as the colloidal solution of cholesterol passes through a damaged arterial tissue and comes in contact with altered tissue colloids and fibrosed anatomic structure resulting from normal aging processes the colloidal state of the transuding cholesterol solution breaks down and cholesterol precipitates or crystallizes extracellularly in the widened tissue spaces. Here the deposition of cholesterol is quite independent of the plasma cholesterol level and may take place in persons with normal cholesterol concentrations. Calcium is frequently also deposited together with cholesterol in the arteriosclerotic tissue, owing to a similar interference by damaged arterial tissue with the colloidal calcium-protein aggregates in the plasma. As Thannhauser points out, however,

> No one would claim that the precipitation of calcium in the arterial wall is a primary disturbance of calcium metabolism, or that the calcium-protein aggregate of itself would cause arteriosclerosis, as is claimed for cholesterol.

Hypercholesteremia with predisposition to atherosclerosis is considered an inborn error of lipid metabolism by Adlersberg.[175] Persons with familial xanthomatosis are assumed to carry two genes responsible for disturbed lipid metabolism; persons with uncomplicated coronary artery disease, a milder form of the same general disturbance, probably carry only one such gene. The gene-induced disturbance is presumed to be in enzymatic chain reactions which lead to abnormal metabolic pathways and result in the accumulation of lipid substances in the blood and tissues.

A finding of potential significance in the serum of many persons with proved coronary artery disease as compared to that of control groups has been elevation of serum cholesterol and serum phospholipids. As emphasized by Steiner and his

associates,[176] however, the increase in serum phospholipids is usually not proportional to the increase in serum cholesterol. Phospholipids have been shown to be naturally occurring emulsifying agents which maintain the lipids of the serum in solution. Consequently, if the cholesterol-phospholipid ratio rises it is theoretically possible that some of the cholesterol may be forced out of solution and hence be deposited in the arteries. Such reasoning applies particularly to coronary patients in whom the cholesterol level is normal but whose cholesterol-phospholipid ratio is elevated. Barr and his group § have shown that most of the cholesterol and phospholipids of plasma are combined with protein in the form of either alpha lipoproteins or beta lipoproteins. Patients who have survived coronary occlusions, or who present otherwise unequivocal evidence of complications of atherosclerosis, frequently show a tendency toward reduction of albumin and alpha lipoproteins and increase in beta lipoproteins. These changes may occur without hypercholesteremia or recognizably significant alteration of the cholesterol-phospholipid ratio. Similar changes in protein and cholesterol distribution may be found in conditions known to predispose to early and extensive atherosclerosis, such as diabetes and familial xanthomatosis. The plasma of young women between the ages of 18 and 35 contains more alpha lipoprotein and less beta lipoprotein than that of men of comparable age. In view of this finding and the well-known fact that women in the childbearing age rarely suffer from coronary disease, the authors have subsequently administered estrogens to certain young patients with coronary disease and within two weeks' time have obtained striking changes in the serum lipoproteins, with distinct elevation of the alpha component and decline of the previously preponderant beta fraction. Of great assistance in this connection is the report of Gertler, Garn, and White describing a coronary profile pattern which permits preselection, with at least a practical accuracy, of young coronary-disease-prone persons. These authors concluded from a three-year study of 97 men who had sustained myocardial infarction prior to the age of 40 that factors making about 7 to 8% of all men susceptible to early coronary disease include an endomorphic mesomorphic body type, serum total cholesterol value of over 309 mg. per 100 cc., uric acid level over 5.4 mg. per 100 cc., and certain other technical biochemical observations too detailed for inclusion here. Additional study will be required, but a cautious optimism seems justified that a prophylactic regimen ultimately may be evolved to protect the atheroma-prone person from catastrophe. On the other hand, of course, it is possible that the sthenic male may consider feminization in any degree a fate worse than death.

Great interest had attended the work of Gofman and his associates,‖ who have made extensive studies of serum lipoprotein fractions by means of an ultracentrifuge technique, recognizing three principle fractions which they designate Sf 12-20, Sf 20-35, and Sf 35-100. Although Keys [185] is doubtful that the method is any more accurate an index of atherosclerotic tendencies than total serum cholesterol determinations, the authors believe that in the cases studied the Sf 12-20 lipoprotein levels show at least a twofold, and up to a possibly tenfold, higher relationship with atherosclerosis than does the total serum cholesterol. The Sf 35-100 class also shows a correspondingly higher relationship with atherosclerosis than does the serum cholesterol. Thus, even for persons with the same total serum cholesterol, be it low, moderate, or high, there is claimed a strong ability of Sf 12-20 and Sf 35-100 lipo-

§ References 177, 178, 179.

‖ References 181, 182, 183, and 184.

proteins to segregate atherosclerotic from normal persons. The authors have found that early recurrence of myocardial infarction in patients with coronary disease is highly related to the Sf 12-20 lipoprotein levels, as is the occurrence of myocardial infarction *de novo* in normals. The depression of high Sf 12-20 levels by dietary restriction of fat and cholesterol has been shown to decrease significantly the chance of recurrence of myocardial infarction in patients with established coronary artery disease (based upon atherosclerosis). In a more recent paper the same observers [186] have reported that heparin suppresses the rise in concentration of Sf 10-50 molecules in the lipoproteins of the human subject. Clinically the administration of 20-100 mg. of heparin produced dramatic relief of angina pectoris in 30 of 32 patients for periods of 3 to 10 days following a single injection. The hypothesis that heparin may play a specific role in lipid metabolism by activating or stimulating the production of a substance in plasma possessing "antichylomicronemic" properties has led Anfinsen, Boyle, and Brown [187] to an extensive study of the mechanism of the heparin effect. The evidence reported thus far tends to show that some material in plasma is converted to "clearing factor" under the influence of a tissue catalyst (most abundant in heart and lung tissue) and in the presence of heparin. The properties of clearing factor suggest that it may be enzymatic in nature. Further studies on purified clearing factor suggest the involvement of an additional "co-protein" acting in the capacity of acceptor or stimulator in the clearing system. In the presence of both clearing factor and co-protein, the Sf 30-150 class of lipoproteins decrease in concentration, with an accompanying increase in the Sf 10-20 lipoproteins. The concentration and distribution of the "normal" Sf 3-10 lipoproteins remains unchanged. Further extension and interpretation of these studies will be awaited with great interest.

Certain other observations merit brief mention before passing on to clinical aspects of coronary disease. The aortas of chickens and rabbits incubated with C^{14}-labeled acetate have been shown by Siperstein and others [188] to synthesize cholesterol about one fourth as efficiently as liver slices, suggesting that endogenous cholesterol originating within the artery itself may play some role in atherogenesis. Arteriosclerosis according to Lansing [189] is a dual process wherein the first stage is senescence and calcification of the elastic tissue in the media; this aging of the arterial wall establishes a substrate where subsequent penetration and accumulation of cholesterol and atheroma formation may or may not occur. After gross and microscopic study of autopsy and surgical specimens from infants, children, and adults who experienced shock, Pollak [190] states that in all such persons hydropic swelling of the intimal endothelial cells of vessels of various caliber was seen. He suggests that following this initial stage seepage of plasma through the defective endothelium causes edema and hyalin-mucoid change of the subintima and that finally, after the breakdown of lipoproteins and resorption of most of the foreign material, the lipids, particularly cholesterol, remain in the subintima, where they act as irritants and initiate the alterations which are generally known as atherosclerosis. Rabbit experiments by Brown and Page [191] have confirmed a "protective" effect of iodide against cholesterol deposition which is independent of the thyroid gland and which seems to be related to the presence of a butanol-insoluble iodine compound in the plasma which may act by altering hepatic cholesterol metabolism. Adlersberg and his associates [192] discuss the occurrence of hypercholesteremia in prolonged courses of cortisone or corticotropin and the possible development of premature

atherosclerosis under these circumstances. Kyle and his collaborators,[193] on the other hand, observe that corticotropin and operative stress reduce blood cholesterol levels, and they suggest that this may represent either a temporary impairment of liver function or, more probably, actual suppression of cholesterol synthesis. Finally, reversing the entire field, it has been suggested by Basu and Stewart[194] that degenerative changes in the vascular system slowly produce abnormalities of the cholesterol level of the plasma, partly by interference with the functional efficiency of the liver and partly by interference with the supply of heparin from the mast cells, which, normally present in the walls of the aorta and of the coronary vessels, these observers found to be absent in three patients with atheromatous changes.

The factors influencing the onset of coronary occlusion and coronary insufficiency have been evaluated by Master and Jaffe.[195] Effort or emotion precedes angina pectoris in almost 100% of cases and coronary insufficiency in about 50%; on the other hand, unusual or severe exertion is associated with coronary occlusion in only 1.9%. Second or subsequent coronary occlusions are purely fortuitous and bear no causal relation to preceding occlusions. The authors believe that in bona fide cases of coronary occlusion starting during or immediately following strain the occlusion has already formed prior to the effort, perhaps asymptomatically, and the strain merely serves to produce symptoms of infarction and even death. Direct trauma rarely results in coronary occlusion, and if there are no symptoms for 48 hours following effort or trauma and a coronary occlusion develops later it is probably not caused thereby. Occupation, season, and the time of day do not influence the incidence of occlusion. The prognosis of coronary disease and particularly of myocardial infarction has been gauged in several large series and has been found to be rather less grave than is generally believed. Among 679 autopsies[196] showing old or recent myocardial infarction (of which 20% were not recognized clinically) the average age at death was 67.8 years. In a group of 124 patients with coronary artery disease followed for at least 10 years, Boas[197] found that the average duration of cardiac symptoms was 13.6 years and that 72% of the group followed their usual occupations during most of their illness. In one series of 182 patients with acute myocardial infarction treated at home by 67 different physicians, Baer and others[198] noted only 8.5% mortality and doubted that bishydroxycumarin (Dicumarol) (given to only 4% in this group) and routine hospitalization are required in all patients. Other large series ¶ indicate that the majority of patients who survive an attack of coronary occlusion or insufficiency are able to lead fairly normal lives and to be gainfully employed and should be encouraged to do so to avoid invalidism. The outlook for an attack, severe or mild, in the elderly patient is no worse than in the young one with similar findings, and the prognosis and efforts at rehabilitation in an individual case should depend on clinical signs and symptoms and not on age. With regard to pain as a guide to prognosis, Behrman and others[201] have observed that long duration of pain, and pain confined to the thorax without radiation, are both associated with higher mortality rate.

Attention has been called to myocardial infarction simulating angina pectoris by Stein[202] in 7 cases and by Wade and Jones[203] in 17. The patients had pain only on exertion, relieved by rest, yet demonstrated electrocardiographic findings consistent with myocardial infarction. Serial electrocardiograms provide the diagnosis. An

¶ References 199 and 200.

unusual instance of myocardial infarction during tetanus antitoxin serum sickness in a 32-year-old man in whom no evidence of organic heart disease was present has been reported by McManus and Lawler.[204] The authors suggest that the serum sickness led to coronary arteritis comparable to that produced in animals by the injection of horse serum. Hyperglycemia occurring in acute coronary thrombosis is a manifestation of shock in which diabetes plays no role, according to Ellenberg, Osserman, and Pollack.[205] Severe shock occasions the outpouring of epinephrine, which stimulates hepatic glycogenolysis; as shock continues the adrenal cortex mechanism comes into play and a sharp increase in gluconeogenesis results. Local anoxia secondary to prolonged vasospasm disrupts hepatic functions and eventually leads to central liver cell necrosis. The same mechanism, although independent of the diabetes, increases the severity of known diabetes with coronary thrombosis. From a study of heart weight in 30 patients with extensive coronary artery disease and no history or pathologic evidence of hypertension, Connolly and Littmann [206] have formed the opinion that cardiac hypertrophy definitely does occur in coronary artery disease, the result of myocardial injury secondary to coronary inadequacy leading to impaired nutrition of muscle fibers. The injury occurs at those times when the demands on the myocardium exceed the available supply; at other times the coronary supply is not only sufficient to meet metabolic needs but is even adequate to permit the development of additional muscle tissue. A glyceryl trinitrate (Nitroglycerine) flicker-fusion test has been proposed by Krasno and Ivy,[207] not only as a potentially valuable diagnostic aid for the presence of angina pectoris and coronary occlusion where the evidence is equivocal but also for the detection and management of persons in whom hypertension or coronary artery disease may later develop. Subsequent reports by other observers,# however, have failed to substantiate the usefulness of this technique so far as a clinical test is concerned.

Notable progress has been made in efforts to raise blood pressure in shock states secondary to myocardial infarction. Intravenous whole blood transfusion on the whole has not improved the mortality rate in such patients [211] and is accompanied by the added risk of congestive heart failure and pulmonary edema,[212] which may be precipitated by a too rapid increase in venous pressure in the face of a weakened heart. Intra-arterial transfusion, however, has been found applicable to patients in shock so severe that the circulation has almost ceased and irreversible damage to such vital organs as heart, liver, brain, and kidneys is imminent. The physiologic mechanisms involved have been described by Jones and his colleagues.[213] Rapid elevation of aortic arch pressure by intra-arterial transfusion under positive pressure reverses the reflex peripheral vasoconstriction attendant upon the shock state and produces a steady flow of blood through peripheral vessels. Normal respiration and urine flow are quickly reestablished. Even more important is the reestablishment of coronary flow, which then favors the restoration of normal or near normal cardiac output and eventual or at least temporary recovery of the patient. Successful application of these principles is reported by Silber and his collaborators,[214] who emphasize the relatively small amount of blood required intra-arterially to restore blood pressure and a normal circulating blood volume. These authors found that intra-arterial infusion had no deleterious effect, even in the presence of pulmonary engorgement, and the resultant improvement in heart condition accompanying the restoration of an effective coronary circulation was often followed by diminution in

References 208, 209, and 210.

pulmonary congestion. Failure of systemic blood pressure to rise with intra-arterial transfusion is an ominous sign indicative of irreversible peripheral vasodilatation or irreparable myocardial depression. Successes have also been reported by Berman and Akman,[215] who prefer a brachial artery exposure, and who emphasize that the improvement in coronary artery perfusion is not only a symptomatic relief but offers a positive therapeutic approach as well. Recently pressor agents,* including l-arterenol and mephentermine, have been found useful in shock with myocardial infarction owing to their property of elevating blood pressure without increase in heart rate or cardiac output or stimulation of the central nervous system. Experience to date suggests that when used cautiously these agents do not worsen and may improve congestive heart failure and pulmonary edema.

In the early part of the period covered by this review, anticoagulant agents were considered to be almost universally indicated in acute coronary thrombosis, witness Wright's statement,

> It is difficult to avoid the conclusion that anticoagulants should be administered to every patient suffering from an acute coronary thrombosis unless the definite contraindications are present.

In contrast, however, comparing a series of 122 cases of bishydroxycoumarin-treated acute myocardial infarction with 128 control cases treated without anticoagulants, Bresnick and his co-workers [219] concluded on practical grounds that bishydroxycoumarin as given under ordinary hospital conditions was largely ineffective in the treatment of acute myocardial infarction. At the same time, Doscher and Poindexter,[220] reviewing 414 cases of myocardial infarction, pointed out that age, sex, preexisting hypertension, angina, and previous infarction materially influenced mortality rates and that consequently the state of the heart at the time of infarction must be weighed in statistical analysis of the effectiveness of bishydroxycoumarin or any other therapeutic procedure. More recently Rytand [221] has felt that there is no valid evidence that prognosis for survival is improved by use of the anticoagulants. The most recent evaluation of the problem is that of Russek and Zohman.[222] Dividing a series of 1,047 consecutive hospital admissions for acute myocardial infarction into "good risk" and "poor risk" groups on the basis of certain serious prognostic signs, the authors found a mortality of 60% among the "poor risks," with an incidence of thromboembolic complications of 10.6%. Among the "good risk" patients, on the other hand, the mortality was only 3.1% and thromboembolic incidents only 0.8%. Further analysis of the 15 deaths among the "good risk" patients showed that at best only 5 of these deaths could have been prevented by bishydroxycoumarin therapy. This theoretical 1% salvage rate is about equivalent to the mortality rate from the use of bishydroxycoumarin itself under average conditions of control. The authors further find that the patient over 60 years of age in either group has no worse a chance for survival than the younger patient in his group with similar clinical findings. In short, the history and the clinical signs and symptoms in any given case, regardless of age, provide the data necessary for prognosis and for decision with regards to the use of anticoagulants.

In addition to bishydroxycoumarin, two other dicumarin derivatives, ethyl biscoumacetate (Tromexan) and 4-hydroxycoumarin anticougulant No. 63, have been found clinically useful.† The hypoprothrombinemic effect of ethyl biscoumace-

* References 216 and 217.

† References 223, 224, and 225.

tate occurs and regresses more rapidly than that of bishydroxycoumarin, but it therefore has the disadvantage in a number of cases of being prone to cause rapid fluctuation in prothrombin levels. Anticoagulant No. 63 produces a more consistent hypoprothrombinemia, fluctuating less from day to day but tending to persist for longer periods after administration of the drug has been discontinued. Experiments with C^{14}-labeled bishydroxycoumarin have shown that the slow recovery of prothrombin levels following the administration of bishydroxycoumarin is due to the fact that the drug is concentrated in and remains in the liver.[226] C^{14}-labeled ethyl biscoumacetate experiments [227] have shown that the mode of action of the two substances is essentially the same, but the quicker, more transient action of the ethyl biscoumacetate is associated with a more rapid and higher liver concentration, paralleled by a higher urinary excretion rate in the first few hours. When vitamin K is injected with bishydroxycoumarin in these observations, the same amount of bishydroxycoumarin concentrates in the liver, but in the presence of the vitamin K the bishydroxycoumarin decreases in concentration much more rapidly. Contrary to earlier opinions, bishydroxycoumarin has been found not to effect the erythrocyte sedimentation rate.‡ Again, in clarification of earlier conflicting reports, water-soluble vitamin K preparations, if given in sufficiently large doses, will accelerate the return of prothrombin time to normal after bishydroxycoumarin has been stopped as efficiently as the oil-soluble vitamin K_1 and K_1 oxide preparations.§ The cases presented by Sachs and Henderson [232] have shown that bishydroxycoumarin may be safely used for patients with chronic renal insufficiency. A reminder, however, of the hazards of anticoagulant treatment is afforded by the cases of hemopericardium, one fatal, reported by Goldstein and Wolff.[233] In conflict with an earlier report, sublingual administration of heparin has been found ineffective by McDevitt and his associates.[234] Gotz [235] has reported the case of a known allergic patient who responded to his first dose of heparin with a severe attack of bronchial asthma associated with giant urticaria, and he believes that this may represent a true hypersensitivity to heparin.

In view of the role of cholesterol discussed earlier in this section, the dietary management of coronary heart disease has drawn attention. In particular, Morrison [236] has emphasized the value of a low-fat low-cholesterol intake of 20 to 25 gm. daily and urges in addition the daily use of lipotrophic substances such as choline and inositol and under certain conditions the employment of hormonal agents. Keys [237] believes as well that a substantial measure of control of the development of atherosclerosis in man can be gained by the avoidance of obesity and even of temporary large calorie excesses and the restriction of all fats to the point where the total extractable fats in the diet are not over about 25 to 30% of the total calories; dietary cholesterol on the whole may be disregarded. Davidson [238] finds no general agreement that choline or inositol have any specific influence on arteriosclerosis or the serum cholesterol level in man and does not believe that it is established that the maximal depression of serum cholesterol level attainable by dietary measures will affect atherosclerosis in man. In any case the degree of dietary lipid restriction necessary to gain this end in some patients may preclude the use of the regimen. Agreeing that the stringencies of the low-fat low-cholesterol diet in many cases

‡ References 228 and 229.

§ References 230 and 231.

outweigh the possible benefits therefrom, Levy [239] further urges that restriction of salt and sodium in cardiac disorders be limited to special instances of hypertension or cases in which there is congestive failure.

A shortening of the period of bed rest in the treatment of myocardial infarction is strongly advocated by Irvin and Burgess.[240] An average of two weeks in bed, with possibly bedside toilet privileges,[241] progressing to walking and light activity by the end of four weeks not only returns the patients to gainful occupation sooner but serves to minimize the physical and psychological disturbances induced by prolonged bed rest. Permitting the patients to rest sitting in an armchair until tired, from the very early days of their infarction on, has been found by Levine and Lown [242] to carry a lower mortality in a series of 81 patients with acute coronary thrombosis than did bed rest and anticoagulant treatment in a somewhat comparable prior series of 138 consecutive patients. The most encouraging aspect of this program was the continued sense of well-being and high morale of the patients, particularly in those experiencing their second or third occlusion. Prompt improvement after being placed in the chair shown by some of those desperately ill with congestive heart failure was especially impressive. In view of the present rather high degree of accuracy of multilead electrocardiography, Littman and Barr [243] suggest that when the findings in an acute coronary episode are less than those of frank classic transmural myocardial infarction efforts should be made to obtain a definite diagnosis of one of the types of acute atypical coronary artery insufficiency, including coronary failure, subendocardial necrosis, and atypical myocardial infarction. In the experience of the authors these latter cases have on the whole a better prognosis and their hospital care and rehabilitation can be considerably less restrictive. Levy [239] counsels against needless restriction on cardiac patients generally, believing that smoking, stair climbing, and ordinary work and exercise may be permitted to the limits of tolerance and common sense. Minor electrocardiographic changes should be minimized whenever possible.

In administering digitalis to a group of 50 patients with proved myocardial infarction without obvious complications, Askey [244] induced no more ventricular ectopic rhythms or instances of sudden death than occurred in a control group of 50 persons treated without digitalis. He therefore concludes that fear of catastrophic arrhythmias should not be a deterrent to the use of average doses of digitalis for early signs and symptoms of congestive heart failure in myocardial infarction. For the fatiguing and sometimes fatal hiccuping complicating infarction, Rubin and others [245] have found that phrenic crush reduces the violence of the hiccups and brings striking relief.

A case of early temporary relief of chest pain in acute coronary thrombosis by spraying the overlying skin of the anterior chest with ethyl chloride is reported by Travell.[246] Later several exquisitely sensitive trigger areas were located in the skeletal muscles of the patient's chest wall, and infiltration with procaine ended the pain entirely. The author believes it highly possible that blocking impulses from the trigger areas in the chest muscles, both with the spray and the infiltrations, contributed toward release of vasospasm in the coronary tree and diminution in reflex ischemia surrounding the infarct, thus reducing the ultimate size of the necrotic area. Raab and Lepeschkin [247] have shown that glyceryl trinitrate counteracts the typical cardioaccelerator and T-wave depressor effects of epinephrine, arterenol, and neurally discharged or injected cardiac sympathin, and they interpret this

phenomenon as being due to an interference of glyceryl trinitrate with the metabolic anoxia-producing effects of the sympathomimetic amines on the cardiac muscle, rather than to the traditional coronary dilator action of glyceryl trinitrate. The studies of Eckstein and his co-workers,[248] however, have led these authors to deny that glyceryl trinitrate, even in large doses, produces any metabolic effect upon the myocardium which can be considered as antiadrenergic. Wègria and his group [249] observed increase in cardiac output per minute, systolic output, and heart rate without blood pressure change during glyceryl trinitrate administration; cardiac work was therefore increased. These findings suggest that glyceryl trinitrate relieves the anginal pain of myocardial ischemia by increasing the coronary flow relatively more than the work of the heart. Extending this concept, the authors point out that glyceryl trinitrate given in the presence of coronary occlusion may actually jeopardize the patient by increasing the work of the heart without being able to increase coronary flow commensurately because of the occluded vessel. On the basis of careful studies in a selected group of 14 patients with angina pectoris, using both oral and intramuscular administration, Hultgren, Robertson, and Stevens [250] have concluded that further clinical use of khellin appears of doubtful value and comment on the high incidence of systemic and local toxic reactions. Other observers|| have had more satisfactory experiences with purified crystalline khellin used intramuscularly, and all agree that further studies, perhaps at higher dosage levels, are indicated. The place of alcohol in the treatment of angina pectoris has been evaluated by Russek and his collaborators,[254] who found that, unlike the nitrites, alcohol has little or no influence on the positive electrocardiographic response to a standard two-step exercise test in patients with angina pectoris. Whiskey did appear as effective as glyceryl trinitrate in preventing anginal pain, however, and these workers concluded that alcohol is not a coronary vasodilating agent but that it is a rapidly acting sedative which increases the threshold of pain, at the same time promoting a sense of well-being. Since the latter combination predisposes to ill-judged overactivity, alcohol may not deserve the position it has traditionally enjoyed in the treatment of angina pectoris. There are reports of improvement in angina pectoris following the use of tetraethylammonium chloride,[255] bilateral stellate ganglion block with buffered ammonium sulfate solution,[256] and roentgen irradiation of the adrenal regions for "sympatheticoganglionitis."[257]

Recording the results of hypometabolism induced by I^{131} in 37 euthyroid cardiac patients incapacitated by angina pectoris or congestive failure, Blumgart and his group [258] noted no serious toxic or untoward reaction and found that one third of the patients had shown rather remarkable improvement and that in another third the improvement was definitely worth while; the remaining third had obtained no benefit. Since this group of patients comprises the intractable cardiac cripples who might be considered for surgery, this medical thyroidectomy, avoiding surgical risks, is promising. Meeting the criticism that the induced hypothyroidism might aggravate any existing tendency toward atherosclerosis, the authors more recently reported [259] another group of severely crippled cardiac patients in whom operative myxedema had been produced and who at autopsy at periods up to 13 years later had

|| References 251, 252, and 253.

no more atherosclerosis than might usually be expected in normal persons of their age. Indeed, in this group there were no complete occlusions, and only three showed slight coronary narrowing.

In a careful injection and dissection study of normal and abnormal human hearts, Zoll and his co-workers [260] have concluded that interarterial coronary anastomoses are organic abnormalities which are a compensatory response to the relative cardiac anoxia which is the common underlying stimulus for such anastomoses in coronary heart disease, cor pulmonale, cardiac hypertrophy, valvular heart disease, and antemortem anemia. Although normal human coronary arteries anastomose anatomically at the capillary level, functionally they are end arteries in that these anastomoses are not of sufficient size and number to be functionally adequate to prevent myocardial infarction after sudden coronary artery occlusion. The great significance then of the interarterial coronary anastomoses which multiply in the presence of anemia and relative coronary anoxia is that these anastomoses are of sufficient caliber to carry adequate blood supplies collaterally around atheromata or even supervening occlusions, preventing or reducing the clinical symptoms and pathological changes following coronary artery occlusion. The variability of the clinical manifestations of coronary artery disease is explained by the interplay of atheroma formation and vessel narrowing on the one hand and the development of interarterial coronary anastomoses on the other. Wiggers [261] holds that, even more important than the stimulus provided by ischemia, the slow establishment of differential pressure gradients which follow partial or complete occlusion of a main coronary branch distends normally useless vessels to such a degree that they become pervious collaterals.

Efforts continue toward a surgical substitute for the naturally but slowly occurring interarterial coronary anastomoses. Introducing talc powder into the pericardial cavity of 36 patients severely disabled with angina pectoris, Thomson and Raisbeck [262] report that the operative mortality was 16% and that, of the survivors, 85% by their own estimate obtained better than 50% improvement, and eight persons considered themselves to be completely relieved and normal. Eleven patients became able to care for their daily needs, and most returned to some form of gainful occupation. Implantation of an internal artery in the left ventricle has been shown by Vineberg [263] to permit dogs to survive subsequent ligation of the anterior descending coronary artery. Two out of three dogs surviving this ligation sustained myocardial infarction and death following ligation of the transplanted artery, suggesting that in these two animals the transplant provided the main supply of blood to the myocardium. Glenn and his co-workers,[264] however, found that the maximal size and numbers of the anastomonic channels in the implantation procedure were found at the end of six to eight weeks after operation. Thereafter these channels underwent gradual fibrosis and regression. After years of extensive animal research, Beck and his associates [265] have developed a two-stage operation for relief of severe angina pectoris. At the first operation an anastomosis is created by means of a vein graft running from the aorta to the coronary sinus. Three weeks later, using special polyacrylonitrile threads, the coronary sinus is partially occluded. The walls of both the graft and the coronary veins thicken after they are exposed to the increased pressure resulting from the anastomosis and take on the appearance of arteries.[266] Applying these techniques at first to severely handicapped humans with advanced coronary artery disease, the authors experienced 8 fatalities in a group of 12 patients. They thereafter selected stronger patients, less severely incapacitated, and have had

generally satisfactory results. Reporting a series of 28 such patients, they note 23 recoveries and 5 deaths, a mortality rate of 18%. Thirteen of those surviving had both stages of the operation and the results to the time of the report were favorable, a number of the patients being definitely enthusiastic about their improvement. There were six instances of thrombosis of the graft found at the second operation, and some of these persons improved following abrasion of the heart and application of a chemical irritant to the pericardium at the second operation. Despite these encouraging results, however, Mason [267] has felt that there is no pathologic proof of the efficacy of a communication between the coronary sinus and the systemic circulation. Zoll and his associates [260] concur.

(To be concluded)

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(To be concluded)

Case Reports

USE OF CORTISONE BY MOUTH IN PREVENTION AND THERAPY OF SEVERE IODISM

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IODIDE reactions are pernicious. Rich [1] described a case in which iodide appeared to cause the destructive lesions of necrotizing arteritis. Deaths due to iodide have been observed, either from angioneurotic laryngeal edema or from exfoliative dermatitis.* In the past therapy for iodide reactions has consisted largely of symptomatic measures, forced fluid, and chloride administration, preferably of the ammonium rather than the sodium salt.

Recently, two reports have appeared on the effect of corticotropin on iodide hypersensitivity. Carey and co-workers [4] described a case of severe iodism, with angioneurotic edema, submaxillary adenitis, and extensive exfoliative dermatitis, in which marked improvement occurred within 48 hours after institution of corticotropin therapy. Cessation of therapy resulted in a recurrence of the exfoliation, which again appeared to be controlled by corticotropin administration. Theodos [5] reported the case of a patient known to be allergic to iodide, in which the ingestion of about 10 ml. of chloriodized oil (Iodochloral) resulted in only a slight reaction while the patient was receiving corticotropin. The alleged beneficial effect of corticotropin in this case was not definite, because of the failure to demonstrate a severe reaction from the same material when corticotropin was not used.

Further documentation of the effect of corticotropin (or of cortisone) on iodide hypersensitivity reactions appears warranted. A case is herein described in which severe iodism appeared to be markedly relieved by orally administered cortisone. The beneficial effect of cortisone appears well established by the subsequent observation that the same amount of iodide as caused the iodism, given as a challenge when the patient was receiving cortisone, caused only a mild reaction.

REPORT OF A CASE

E. D., a 55-year-old white man, was admitted to the hospital, in March 1953, because of a perennial cough, which was productive of moderate amounts of mucopurulent sputum. During the seven months before admission he had wheezing dyspnea. In March 1952 a bronchogram performed at another hospital reportedly showed no evidence of bronchiectasis.

Physical examination revealed a middle-aged white man in no acute distress. The positive physical findings were a blood pressure of 170/98, an increased anteroposterior diameter of the chest, and diffuse sibilant and sonorous musical rales with asthmatoid breath sounds bilaterally. The patient was able to raise sputum which was grossly mucopurulent.

Laboratory examination showed a normal blood cell count, a corrected sedimentation rate of 33 mm. per hour, and a blood urea nitrogen level of 20.8 mg. per 100 ml. The urinalysis was

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* References 2 and 3.

not remarkable except for a maximum specific gravity of 1.010, which was demonstrated by a Fishberg concentration test. An electrocardiogram was within normal limits. Roentgen ray examination of the chest showed slight flattening of the hemidiaphragms and mild elongation of the aorta. Bronchoscopic examination revealed diffuse hyperemia of the tracheobronchial tree without evidence of obstruction or ectasia.

Diagnoses were made of severe chronic bronchitis, pulmonary emphysema, and benign hypertensive vascular disease with nephrosclerosis.

During the hospital course of this patient, the following phenomena were observed. Fifteen drops of a saturated solution of potassium iodide was administered in water twice during a three-hour interval. Mild paresthesias about the tongue developed shortly before the second dose of iodide. Within a few hours, there ensued pain in the subglottic region and marked swelling under the patient's tongue and in the submaxillary regions. Coryza, coughing, emesis,

Fig. 1.—Massive enlargement of the submaxillary and sublingual glands after the patient received two doses of potassium iodide.

and slight fever occurred. One grain (60 mg.) of codeine, 50 mg. of tripelennamine (Pyribenzamine), and 50 mg. of diphenhydramine (Benadryl) caused little if any symptomatic relief.

Upon examination, massive tender enlargements of the patient's sublingual and submaxillary glands were found. This marked adenitis is well illustrated in Figure 1, which was taken 19 hours after the first administration of iodide. There was concomitant edema of the nasal mucosa.

Results of Cortisone Administration.—Nineteen hours after the initial dose of potassium iodide the patient was placed on a low-salt diet and 100 mg. of cortisone was administered orally. The patient's symptoms soon improved. In six hours another 100 mg. of cortisone was given. The dramatic improvement of the patient nine and one-half hours after institution of cortisone therapy is illustrated in Figure 2. At this time pain and distress were absent, the patient feeling markedly better and afebrile. The sublingual and submaxillary glands were but mildly swollen. The next day an additional 25 mg. of cortisone was given. The salivary adenitis and coryza continued to resolve. Ammonium chloride was then administered for several days, with entire disappearance of the signs of iodism.

Fig. 2.—Marked resolution of the sialadenitis nine and one-half hours after institution of oral cortisone therapy.

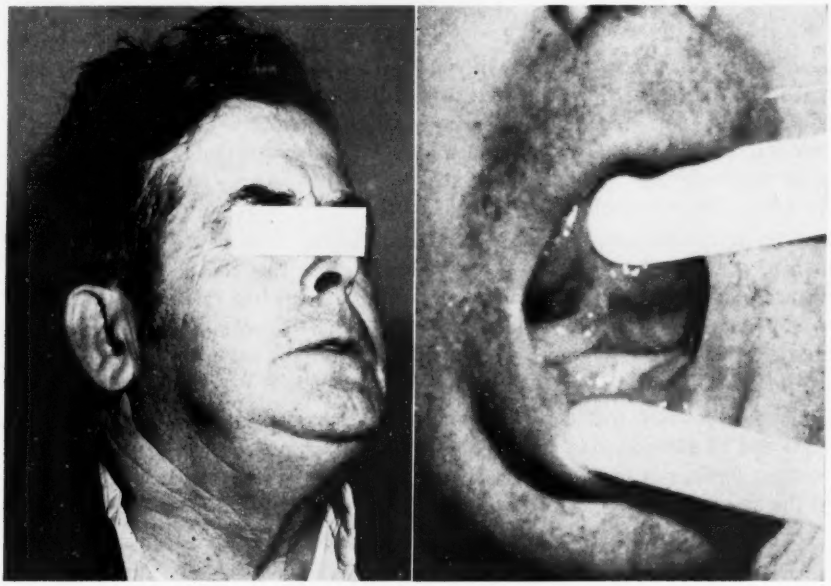

Fig. 3.—The effect of cortisone in preventing severe iodism. The patient had taken the same amount of iodide as was given before Figure 1 was made.

Six and a half weeks after the above-described episode of severe iodism the effect of prophylactic cortisone by mouth on this patient's iodide hypersensitivity was investigated. No iodide compounds had been administered during this interim.

The patient was again placed on a low-salt diet, and 50 mg. of cortisone was given orally every six hours for three doses. Six hours later 100 mg. was administered. This cortisone was followed, in two and five hours, by 15 drops of saturated solution of potassium iodide in one-half glass of water. The six-hour schedule of cortisone in 50 mg. amounts was continued for two more doses. Then the amount was reduced to 25 mg. and, after one dose, was given at eight-hour intervals during the next 24 hours. Twenty-five milligrams was given twice the next day and once the subsequent day.

Slight paresthesias under the tongue developed two hours after the first ingestion of iodide. The patient's symptoms remained slight for the next few hours. The height of this iodide reaction was gradually reached approximately 14 hours after the initial iodide administration. Fever did not develop. Coryza, lacrimation, and hoarseness were moderate. There were slight periorbital edema, edema of the nasal mucosa, and mild injection of the palpebral conjunctivae. The submaxillary and right sublingual glands were only mildly swollen and tender, while the left sublingual glands were within the upper limits of normal size. The state of the salivary glands during the height of this reaction is illustrated in Figure 3. The slight enlargement of the sublingual and submaxillary glands contrast markedly with the massive iodide sialadenitis illustrated in Figure 1, found previously when cortisone had not been used.

Twenty-four hours after the first dose of iodide the physical signs remained mild to slight. By the next day the patient was essentially asymptomatic and the salivary glands were normal in size except for minimally swollen right sublingual glands. These gradually assumed a normal size.

Careful inquiry revealed that the patient had experienced a clinical picture of severe sialadenitis after the bronchogram, utilizing iodized oil, U. S. P. (Lipiodol), done the year before. The patient also stated that tincture of iodine had caused a dermatitis when applied topically. Idiosyncrasy to iodide was thus confirmed.

COMMENT

The apparent efficacy, herein described, of cortisone therapy for a severe iodide reaction was confirmed by the demonstration that cortisone, administered before and after the same amounts of iodide, was associated with the development of only mild iodism. It thus appears demonstrated that iodide reactions can be alleviated by cortisone therapy. This augments the case report of Carey and co-workers [4] on the effect of corticotropin on iodide sensitivity.

The implications are both theoretical and practical. The nature of iodism is not known. Various theories have been proposed, e. g., that iodism is caused by a disturbed colloidal equilibrium in body fluids, by an increased vascular permeability, by autolysis, or by anaphylactoid reactions.[6] The demonstration that cortisone alleviates iodism is in accord with, but does not prove, a hypersensitivity basis for iodism.

The observation that cortisone prevented severe iodism from developing suggests that by administering cortisone prophylactically roentgenography with iodized contrast media can probably be safely performed in persons known to be allergic to the same material.

The demonstration that cortisone by mouth alleviates severe iodism augments the therapeutic armamentarium for iodide reactions. This need for effective therapeutic measures is particularly great for a substance as widely used as iodine, which, both for diagnostic purposes and for therapeutic uses, is extensively employed and for which the threat of idiosyncrasy remains.

SUMMARY AND CONCLUSIONS

A case is described in which orally administered cortisone appeared to alleviate severe iodide hypersensitivity.

Orally administered cortisone also prevented the development of severe iodism.

Cortisone should prove a valuable adjunct in the treatment of severe iodide reactions.

ADDENDUM

After this paper was submitted for publication, a case was reported in which but 50 mg. of intramuscularly administered corticotropin appeared to prevent iodism following bronchography. (Park, F. R.; Cronk, R. T., and Cronk, G. E.: Prevention of Iodism in Bronchography by Use of ACTH: Case Report, *Dis. Chest* **24**:219, 1953). Only a week before, the patient had manifested severe iodism after a similar bronchographic procedure with the same amount of iodized oil. It is suggested that the initially administered iodized oil may have been sufficient to have desensitized the patient to the iodine which was given one week later.

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PAROXYSMAL COLD HEMOGLOBINURIA IN TREATED CONGENITAL SYPHILIS

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IT IS KNOWN that paroxysmal cold hemoglobinuria occurs most frequently in persons with congenital syphilis. The case to be presented is of particular interest because the patient was born and raised in the subtropical climate of Hawaii. The manifestations of hemoglobinuria did not occur in any degree of severity until he was exposed a cold climate, as was that in Korea.

REPORT OF CASE

A 22-year-old Hawaiian man was referred to our hospital on Jan. 12, 1952, because of a history of voiding dark-red urine. Four days prior to admission the patient felt unusually cold and chilled and voided port-wine-colored urine. He reported to the local dispensary on the same day, but physical examination and subsequent urine specimens failed to reveal any abnormality. The patient was asymptomatic until Jan. 12. On that day, while en route to the hospital, he was exposed to the cold for about two hours. Subjectively, he felt cold and experienced a chill. The urine specimen collected on arrival at the hospital was port wine in color. The patient had been exposed to the winter weather in Korea for the previous one and one-half months. Except, however, for these two episodes he had not become chilled or felt excessively cold or ever passed a dark-red urine.

The patient was born in Hawaii and had never left that area until his present tour with the Army. He recalled that when he was a child, one day when the temperature was cooler than normal, he felt cold and experienced a chill and passed Burgundy-colored urine. He also recollected that if he remained in the ocean for too long a period of time bumps would develop on his skin. These eruptions disappeared upon rubbing. He does not recall whether they were pruritic or not.

Past History.—The patient was known to have had congenital syphilis and was treated with heavy metals and penicillin in 1947. A lumbar puncture was performed the same year and was reported as showing no abnormality. In 1951, at the induction center, a lumbar puncture was performed and the tests were equivocally positive for syphilis. Two subsequent examinations of the spinal fluid revealed no evidence of syphilis, and therefore he was accepted for military service.

Family History.—The patient's mother and sister were both known to have syphilis and were treated with heavy metals and penicillin in 1947. The patient's father and three siblings were living and are well and were not reported to have had syphilis. No other members of his family had ever had any episodes of voiding dark-red urine.

Military History.—The patient had been in the Army for seven months, was trained in Hawaii, and was then assigned to the Far East Command and had been stationed in Korea for one and one-half months prior to his hospital admission.

Physical Examination.—The patient, a Mongolian, was in no acute distress and was well developed and well nourished. Blood pressure, 146/82; pulse, 80; respirations, 18; temperature, 98 F. Skin was normal; ears normal; pupils round, regular, and reacted to light and in accom-

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modation; cornea normal. There were no abnormal lenticular or funduscopic findings. No Hutchinson teeth or mulberry molars were observed. The nose, bridge of nose, and nasal septum were all intact. The pharynx was normal; the tonsils were present and not enlarged; the palate and mucous membranes were normal. The lung fields were resonant, and no abnormal breath sounds were heard. Heart: apical impulse was diffuse but area was normal in size to percussion; no thrills were felt or murmurs heard; sounds were of good quality, and A_2 was greater than P_2. The abdomen was soft and nontender; the liver and spleen were not palpable. On the previous afternoon, however, the admitting physician described a palpable nontender liver edge 3 to 4 cm. below the right costal margin. The genitalia were normal. Rectal examination was not remarkable except that the prostate was enlarged one to two times. The extremities were normal except for traumatic scars. Neurological examination revealed no abnormalities.

Laboratory Findings.—On the day of admission the urine was dark-red and opaque, acid, and showed a 4+ reaction for albumin, a trace of sugar, and a 1+ reaction for bile. Microscopic examination showed 4+ amorphous urates, occasional course granular casts, and a few WBC's per high-power field. Addition of the urine to the benzidine reagent resulted in a 4+ reaction. Hemoglobin was 11.0 gm., RBC 3,050,000, hematocrit level 34%, WBC 7,650, with polymorphonuclear cells 56, lymphocytes 40, and eosinophiles 3. The blood Wassermann and cardiolipin tests were negative. Roentgenograms of the chest, skull, and long bones showed no abnormalities. Tests for cold agglutinins were negative.

Progress.—The patient was asymptomatic and afebrile throughout his hospital course. Within 24 hours his blood pressure decreased from 146/82 to 128/64 and remained within that range. The morning after admission the urine was yellow, cloudy, and acid; tests for sugar and albumin were negative; specific gravity was 1.012. Microscopic examination showed 2 to 3 WBC's per high-power field. Chemical analysis revealed 1+ bile and 1+ urobilinogen, and no hemoglobin pigment was present. NPN was 28 mg. per 100 cc.; icteric index, 16; no hemolysis was detected in the serum. On the second hospital day the urine was normal. On the third hospital day hemoglobin was 13 gm.; RBC 3,440,000; hematocrit level, 39%; WBC 9,400, with polymorphonuclear cells 53, lymphocytes 44, monocytes 2, and basophiles 1; no hemolysis was noted in the plasma. On the fourth hospital day the icteric index was 10; on the fifth day a Donath-Landsteiner test was performed. Within 20 minutes after warming the patient's blood to 37 C., hemolysis was observed, whereas the two controls showed no hemolysis. After two and one-half hours there was moderate hemolysis of the patient's blood and the controls were still negative.

On the following day, Jan. 18, the patient's hands were immersed in a water bath varying from 7 to 12 C. for 20 minutes. Three hours later the patient was observed to be wrapped in a blanket and shivering slightly. Subjectively, he felt cold and chilled. All urine specimens were examined for the next 48 hours, but no abnormal findings were noted. On Jan. 19 the serum was reported as showing slight hemolysis. Hemoglobin was 12.5 gm.; WBC 8,650, with a normal differential cell count; icteric index 9.9.

In view of the negative serology and lack of any clinical symptoms, no treatment was administered. On Jan. 24 the patient was evacuated to a general hospital for medical board disposition.

COMMENT

This patient demonstrated many classic features of paroxysmal cold hemoglobinuria and manifested symptoms despite the fact that he had been successfully treated for congenital syphilis.

It is interesting to note that the patient gave a history of an urticarial-like rash when he was exposed to the cold ocean water. One can postulate a circulating dermatolysin, as described by Harris, Lewis, and Vaughan.[2]

On admission a transient elevation of the blood pressure was noted, as well as a palpable liver. These signs disappeared within the first 24 hours. The laboratory data confirmed the findings of hemolysis: the transient rise of the icteric index, the urobilinogen and bile in the urine, and the hemoglobinuria. The positive Donath-Landsteiner test confirmed the diagnosis and demonstrated the phenomenon in vitro.

An in vivo test was performed, and the only objective evidence was the observation of hemolysis in the plasma. Subjectively, the patient described a chilled feeling about three hours after the exposure to the cold water. These symptoms were the same as he had experienced during the two previously described attacks. The urine, however, did not show the presence of hemoglobin pigment. The former results could be questioned as possibly due to a laboratory error. It is possible, however, that the hemoglobin in the circulating plasma was not of high enough concentration to be found in the urine.

It is stated in many reports that with adequate antisyphilitic therapy the episodes of hemoglobinuria when the patient is exposed to the cold will no longer occur. In our case adequate therapy, which included penicillin and heavy metals, was given. The blood cardiolipin and blood Wassermann tests were negative, and there were no objective signs of infection.

This syndrome has been reported in both acquired and congenital syphilis.

SUMMARY

A case of paroxysmal cold hemoglobinuria in a patient who had had a successfully treated congenital syphilis is presented. It is of interest because of the lack of symptoms in a subtropical climate and the manifestations of the pathology while on duty in Korea during the winter months.

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News and Comment

ANNOUNCEMENTS

Second National Conference on Trichinosis.—The Second National Conference on Trichinosis will be held in the auditorium of the American Medical Association, 535 N. Dearborn St., Chicago, on Monday, March 1, 1954. Further information may be obtained from S. E. Gould, M.D., Chairman, Wayne County General Hospital, Eloise, Mich.

Mexican National Institute of Cardiology.—The Second Congress of the Sociedad de Internos y Becarios del Instituto Nacional de Cardiología de México will be held in Acapulco, México, April 21-24, 1954.

This international congress will be the culmination of the festivities, to be held on April 20, in commemoration of the tenth anniversary of the founding of the Instituto Nacional de Cardiología. Further information may be obtained from Dr. Jorge Soberón Acevedo, Sociedad de Medicos Internos Residentes y Becarios, Avenida Cuauhtemoc No. 300, México, D.F., Mexico.

Symposium on Venereal Diseases.—The Sixth Annual Symposium on Recent Advances in the Study of Venereal Diseases will be held in the auditorium of the Department of Health, Education, and Welfare, Washington, D. C., on April 29 and 30, 1954, it was announced by Dr. James K. Shafer, Chief of the Public Health Service, Division of Venereal Disease.

The sessions are open to all physicians and workers in allied professions who are interested in participating. These symposia usually draw hundreds from all parts of the country and are the occasion for exchange of the latest available information by some of the outstanding authorities in the field of venereal disease.

The topics that will be discussed at this symposium will cover many aspects of venereal disease control, including basic and clinical research, serology, epidemiology, treatment, program operation, and professional education.

Sixth World Congress for Welfare of Cripples.—Persons from all parts of the world interested in services for the disabled will assemble at The Hague, Netherlands, from Sept. 13 to 17, 1954, for the Sixth World Congress of the International Society for the Welfare of Cripples (ISWC), it was announced by Donald V. Wilson, Secretary General of the Society.

Representatives of the 26 national organizations which are members of the International Society are expected to attend the Congress, as well as representatives of the United Nations, World Health Organization, and other governmental and nongovernmental organizations interested in services for the physically handicapped.

The Congress will be held under the joint auspices of the ISWC and the Netherlands Central Society for the Welfare of Cripples, the affiliated national organization in the Netherlands of the ISWC.

The program will present through plenary sessions, demonstrations, panel discussions, and special meetings analyses of developments throughout the world in services for the disabled and means for furthering such services in the medical, social, educational, and vocational fields.

Mr. J. M. Ravesloot, President of the Netherlands Society and Mayor of the city of Almelo, has been designated president of the Sixth World Congress.

The International Society for the Welfare of Cripples is a federation of national voluntary organizations providing services for physically handicapped children and adults. Founded in 1922, it has, for many years, been the outstanding organization of its type in the international field.

The Society's program includes all phases of rehabilitation of the disabled—prevention, medical services, education, social services, therapy, recreation, and employment. It serves as

an international clearinghouse for information concerning technical and social developments in rehabilitation services for the handicapped.

The services of the Society are extended to persons and organizations throughout the world, both member and nonmember, who are engaged in work for the benefit of the handicapped. The affiliated member in the United States is The National Society for Crippled Children and Adults, which has headquarters in Chicago. The central offices of the International Society for the Welfare of Cripples are located in New York. Mr. Konrad Persson, Director General of the Royal Pensions Board and Chairman of the Norrbackainstitute in Sweden, is president of the Society.

First International Conference on Thrombosis and Embolism.—The date of the First International Conference on Thrombosis and Embolism, to be held at the Universitäts-frauenklinik, Basel, Switzerland, has been changed to July 20-24, 1954. Applications for participation should be addressed to the General Secretary of the First International Conference, at the above-mentioned address, or to an agency of the American Express Company.

The International Convention of Gynecologists will be held in Geneva immediately following the Conference on Thrombosis, July 26-31, 1954.

Books

Human Factors in Air Transportation: Occupational Health and Safety. By Ross A. McFarland, Ph.D., associate professor of industrial hygiene, Harvard School of Public Health. Price, $13.00. Pp. 830, with many tables, diagrams, and illustrations. McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 18; Aldwych House, Aldwych, London, W.C. 2, 1953.

This is an important book. It is divided into nine parts. After a short introductory chapter there are chapters dealing with selection and training of flight personnel, maintenance of health and efficiency of flight personnel, selection of ground personnel, safety on the ground and in flight, sanitation and health in airline operation, passenger and service problems, and, finally, a chapter on health and medical services in air transportation.

Each chapter is well written and contains at the end a summary of the content of the chapter as well as a selected bibliography. Thus the entire volume opens the door for any reader to practically every phase of aviation medicine.

The author is an authority on aviation. More than that, he is gifted as a writer, so that each chapter of his book tells its story in an interesting, delightfully readable fashion. One can learn how fliers are selected, how passengers are cared for, and the notably low risk of flying even to persons with well-marked cardiovascular diseases or to those who are very old or very young, and one can learn, too, of the complex studies in physiology, engineering, and public health that have been completed in order to bring air transportation to its present degree of safety and usefulness.

Any reader will find the book interesting. To a doctor, it is a new kind of textbook, designed to supply him with information on all medical aspects of life in the air. It is an outstanding work; it deserves highest praise and, certainly, a place in every medical library.

The Biochemistry of Gastric Acid Secretion. By Edward J. Conway, M.D. Price, $6.50. Pp. 183, with 37 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

Dr. Conway's text is an excellent review of the chemical mechanisms involved in the formation of acid by biological systems in general and by the parietal cell of the gastric mucosa in particular. As the author has clearly indicated in the title, the book is directed specifically towards the biochemical mechanisms associated with production of acid in the parietal cell. Dr. Conway develops fully his concepts of the parallelism between the formation of acid by yeast

cells and parietal cells. Although the parallelism is admittedly incomplete, the similarities are sufficient to have enabled him to study in detail many of the chemical processes involved. The book is slanted definitely, as it should be, in the direction of Dr. Conway's own interpretations of the data currently available. His concepts are clearly presented and deserve the attention of all students seriously interested in the production of acid by the parietal cells of the gastric mucosa.

Gout and Gouty Arthritis. By John H. Talbott, M.D. Price, $4.00. Pp. 92, with 24 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

This 80-page monograph is modeled after the original 130-page reprinted monograph which was published in Oxford Loose-Leaf Medicine. In this second monograph the history of gout is briefly discussed and the incidence, predisposing factors, and the influence of hereditary predisposition to gout are briefly presented. The intermediary metabolism of uric acid is discussed in detail, with the recent utilization of isotopic compounds. The pathologic anatomy is comprehensively reviewed. There are 24 excellent photographs of x-rays of gouty changes in the various stages of the disease. The classification, symptoms, and complications are presented in brief but are extensive enough for a practical discussion of the essential important details. The chapter on treatment includes the newer agents, corticotropin (ACTH), cortisone, probenecid (Benemid), and phenylbutazone. In discussion of the diet in gout the author questions the stigma of proteins in the pathogenesis of gout on the basis of his own work and that of others with isotope techniques.

This brief monograph has outlined the important etiological, pathological-anatomical, clinical, and newer research data on gout in an easy-to-read style. The treatment is, likewise, comprehensive but brief. The reviewer recommends this monograph to internists and rheumatologists.

Endocrine Treatment in General Practice. Edited by Max A. Goldzieher, M.D., and Joseph W. Goldzieher, M.D. Price, $8.00. Pp. 474. Springer Publishing Company, Inc., 44 E. 23rd St., New York 10, 1953.

This book was written by 21 clinicians and is designed as a reference book for the general practitioner. It is divided into general subject headings considering disorders related to age, disorders of metabolism and nutrition, disorders of organ systems, disorders of resistance, neoplastic diseases, and a complete catalog of currently available hormone preparations. All subjects are completely covered, with very little overlapping. This should be a very useful reference book.

Introduction to the Interpretation of the Electrocardiogram: With Sixty-One Plates Illustrating the More Important Deviations from the Normal, Selected from the Files of the Michael Reese Hospital. By L. N. Katz, M.D.; R. Langenedorf, M.D., and A. Pick, M.D. Price, $2.50. Pp. 77, with 67 illustrations. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1952.

In the preface the authors state that this paper-bound booklet should be particularly suitable for the physician whose specialty lies outside the field of cardiology and for the student who is beginning his studies in cardiac physiology. The book begins with a short discussion of the genesis of the electrocardiogram and the theoretical aspects of vectorcardiography. If the latter subject does not become completely clear to the reader in the few paragraphs devoted to it, at least he will not be completely confused.

The remainder of the small book describes briefly the technique of reading electrocardiograms and the procedures to be followed in interpreting them. A long series of illustrations of normal and abnormal electrocardiograms with the author's readings and explanations follows. The discussion of disturbances of location of impulse formations and abnormal rhythms is particularly useful. After that, the abnormal patterns suggesting specific etiology are very adequately discussed. The book will be a valuable acquisition for those not specially trained in cardiology, for it gives in brief and easily understandable form the essentials that should enable any physician to recognize the more important aberrations which electrocardiograms disclose.

Medicine: The Patient and His Disease. By A. E. Clark-Kennedy, M.D., F.R.C.P. Second edition. Price, $6.00. Pp. 410. E. S. Livingstone, 16 and 17 Teviot Place, Edinburgh 1, 1953.

Many years of teaching and clinical experience have prompted the author to undertake a philosophical essay correlating the multiple facets of medical science and practice. In effect he has conducted a "guided tour" through the entire field of medicine, avoiding statistical data while interpreting disease processes with rare insight and simplicity.

His book, by intent, is not a text or a reference. Rather it is intended to provide perspective and mutual understanding among the specialties. Thruout his writings, the author has clearly maintained an attitude of human understanding and philosophical calm, while discussing with equal ease and familiarity the most complex and remote subjects or the commonest aspects of medical practice.

For the bewildered student, the harassed practitioner, or the confined specialist, this book should provide refreshing insight and renewed zest for the study of medicine.

Synovial Fluid Changes in Joint Disease. By Marian W. Ropes, M.D., and Walter Bauer, M.D. Price, $4.00. Pp. 150, with illustrations. Harvard University Press, Cambridge 38, Mass., 1953.

This book is a monograph which presents the data which have been gathered in 20 years of study of synovial fluid in 1,500 examinations of joint fluid, chiefly from the knee joint, in patients seen at the Massachusetts General Hospital.

The authors first discuss the normal values of some of the characteristics of the joint fluid, such as pressure, amount, total and differential cell counts, and the amount of protein and mucin present in the fluid.

Using these values as a baseline, the authors then discuss and tabulate the changes in these characteristics as they occur in all the known disorders of joints. For this purpose, they divide all such diseases into two groups: Group 1, those conditions of traumatic origin, and Group 2, those of infectious origin and rheumatoid arthritis. They stress the importance of repeated aspiration of joints, for both therapeutic and prognostic reasons. They also consider the value of such determinations of joint fluid in the differential diagnosis of these disorders.

Although the monograph has many tables and is full of figures and data, it is well organized and presented. It should be in the library of all physicians and research workers who are interested in the physiology and/or pathology of joints.

Practical Blood Grouping Methods: A Manual of Immunohematology. By Robert L. Wall, M.D. Price, $5.00. Pp. 176. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

This monograph is an attempt to assemble the many divergent techniques related to the field of blood grouping and present them in a manner which physicians and technicians interested in this subject may understand. The multitude of blood groups are given in the chronology of their discovery, and subsequent sections of the monograph deal individually with each blood group system and the techniques applicable to this system. Where more than one method is acceptable, the author has attempted to choose and justify his choice. Many of the rarer blood groups are dealt with, excluding a few recent blood groups identified on the basis of one antiserum. An especially valuable chapter deals with the methods, materials, and laboratory jargon as it applies to this subject, with special attention to the estimations of endpoints and safeguards in evaluating antiserums.

The section on Rh blood groups has employed the use of the Fisher-Race nomenclature, which the author justifies by his opinion that it is more easily grasped by the student and by the report of an impartial committee on nomenclature, which is contained in the appendix. Separate chapters on cross-matching, antibodies in hemolytic anemias, and differential agglutination tests for estimating the survival of transfused erythrocytes suggest a few of the applications of these

immunohematologic techniques. The appendix describes methods of preparing specific antiserums and their assay. A section on methods of erythrocyte modification by trypsin, periodate, and other agents is included.

The bibliography is selective in that it contains only 145 items in a field in which many thousand papers have been written.

Wherever possible controversies have been avoided, and where this is impossible both sides have been presented.

The volume is highly recommended as a presentation of a difficult subject in an easily understood, simplified manner.

The Medical Clinics of North America: Nationwide Symposium of Bedside Management (July-August, 1953). By many authors. Price, $12.00, or $16.00 yearly. Pp. 326, with 169 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

Following the usual custom, this issue of the "Medical Clinics" is mainly concerned with ". . . some of the more common problems encountered in the daily practice of medicine." The present issue is the Nationwide Symposium on Bedside Management.

The opening chapter, on management of cardiac emergencies, by Harold D. and Samuel A. Levine, is a complete discussion of the complications of myocardial infarction, acute pulmonary edema, pulmonary embolism, hemorrhage due to use of anticoagulants, air embolism, and cardiac resuscitation. The chapter following—Treatment of Cardiac Decompensation—is concerned mainly with those cases of heart failure which are resistant to the ordinary means of treatment; it is by T. M. Durant, of Temple University, and W. T. Harvey, of Denver. A resumé of the pharmacology, indications, dosage schedules, precautions, and results with the use of hexamethonium chloride and 1-hydrazinophthaline (Apresoline) for arterial hypertension is written by H. A. Schroeder and J. D. Morrow, of the Washington University. H. G. Wolff and M. M. Tunis, of the New York Hospital-Cornell Medical Center, have made a good review of the confusing subject of headache, with an etiologic classification, a discussion of headache mechanisms, and details of treatment. In "Management of Anemias" by M. M. Wintrobe and G. E. Cartwright, of Utah, light is thrown on a problem which is still often mismanaged by many physicians.

There are other articles on management: rheumatoid arthritis, acute rheumatic fever, backache, skin disease, ulcerative colitis, liver disease, acute burns, nephrosis and acute glomerulonephritis, thrombophletitis and phlebothrombosis, diabetes mellitus, amenorrhea, bronchial asthma, bronchiectasis, pneumonia, and toxic goiter.

The volume contains some of the best of current thought on treatment of common diseases.

Physical Examination of the Surgical Patient. By J. Englebert Dunphy, M.D., F.A.C.S., and Thomas W. Botsford, M.D., F.A.C.S. Price, $7.50. Pp. 326, with 188 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

This volume of physical diagnosis is, as stated in the title, limited to the "surgical patient." The information is, however, nonetheless valuable for all those concerned with differential diagnosis. For the authors, in a logical informal manner, weave the little-known procedures of diagnosis with familiar methods into a composite and then discuss the important differential considerations in terms of the physical findings. Though the book is one of procedures, methods, and signs, the authors have included with rare facility useful details, valuable classifications, and significant commentaries.

The book is divided into two portions, the examination of the acutely or chronically ill patient and the emergency examination of the desperately ill. The "elective" examination studies the patient in the classical order but with the forementioned considerations. Special comment is made of the study of the postoperative patient with emphasis on the postoperative chest or abdomen. Valuable commentaries are also made about the extremities regarding their evaluation for peripheral arterial and/or venous disease, ulcers, or gangrene. A chapter is

devoted to the methods of examination of infants and children. The emergency examination division includes in addition to general principles a discussion designed to develop a more rapid and accurate appraisal of injuries about the head and neck, thorax, heart and lungs, abdomen—gastrointestinal and genitourinary, spine, and extremities.

The book is well written, being clear and concise, and is well illustrated both regarding findings and methods of eliciting them. A bibliography is included at the end of the book, but no references are given for individual techniques, methods, or signs. It should prove of material aid in reaching a more accurate diagnosis by physical means for all, but especially for the internist, the surgeon, and the general practitioner.

Shock and Circulatory Homeostasis. Edited by Harold D. Green, M.D., with many contributors. Price, $3.50. Pp. 245. Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1952.

The transactions of the First Conference on Shock and Circulatory Homeostasis, sponsored by the Josiah Macy, Jr., Foundation, form the contents of this book. Data are presented by some of the leading investigators in this field and are thoroughly discussed and evaluated.

Only certain aspects of the problem of shock are presented, such as humoral, vasoactive, and other metabolic derangements in shock; the nervous system in shock; acute and chronic hypotension after hemorrhage in man; the infectious element in shock, and the therapeutic implications of current concepts of shock.

This presentation points out some of the problems in shock and some of the approaches in current investigation. There is no clear definition of shock nor is there agreement on the significance of various aspects of shock as presented in this book. The extent of the defects in knowledge of this syndrome is rather clearly indicated.

This book should be of considerable interest and value to both investigators and clinicians.

Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems; Transactions of the Ninth Conference, March 20-21, 1952. Edited by Heinz von Foerster. Price, $4.00. Pp. 184, with 25 illustrations. Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1953.

The average physician is apt to feel very ill at ease when discussion of cybernetics comes up, and not without reason. For some who do not feel concern there may be confusion. To an extent both of these may be resolved in part by thoughtful reading of the Josiah Macy, Jr., Foundation's "Transactions of the Ninth Conference on Cybernetics," which is now published in book form. This book is an edited transcript of a small meeting in which a number of devotees of the fields of cybernetics presented papers and much informal discussion. There was a healthy give and take, a certain amount of argument, and perhaps because of the nature of the meeting there was a good deal more humility than is expressed in the published pontifications of some of the people who participated in the conference. It might be well for the casual reader to have some background and review the previously published transactions. Such is not necessary, and one can get a good view of the themes and postulates of the philosophy of cybernetics from this book. Since this is an interdisciplinary effort between mathematicians, electronics engineers, social scientists, psychiatrists, neurologists, anthropologists, and statisticians, their common necessity for intercommunication has reduced some of the chance for error and misconstruction by the simple expedient of interrupting questions when the going gets tough. For whatever insight into the mysterious workings of the central nervous system may be contributed by electronic machines we should be duly grateful. The real danger is that the enthusiasts follow the philosophy of Procrustes to fit by hook or crook the observed data into their preconceived concepts. As one might expect, there is very considerable unevenness in the book. One of the most remarkable spectacles is a rather severe and humorless discussion of the position of humor in human communication. Emotions and feed-back concepts are dealt with with the restraint not always seen in such discussions. A great danger encountered in the philosophical ruminations of a group such as this is the fact that by and large in spite of their diverse and various educations they have come into the conference with no deep-grained wisdom concerning the problems of Western philosophy. This is particularly true when they come to deal with such

concepts as universals and whether self-re-exciting loops of neurons can know universals and the subtle interconnections of mind and brain that puzzle the deepest philosophers. At times the critical point of separation seems to have eluded one or another of the participants. Thus the main hazard in the field of cybernetics now is that the facile formulations of the brilliant electronics engineers be too readily accepted as a satisfactory model or facsimile of the workings of the most complicated structure we know anything about—the human brain. Perhaps it is not unreasonable to sum up the problem by a statement in comment about one of the complex machines by one of the participants, "It may be a beautiful replica of something, but heaven only knows what."

Bakteriologische Nährboden. By Lothar Hallmann, M.D. Price, 19.80 d.m. Pp. 252, with 52 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a), Stuttgart, Germany, American agent Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

This is a first edition of a German monograph on the preparation of selected culture media most frequently used in the medical bacteriologic laboratory.

The book is divided into two parts, the first of which contains valuable data on basic principles involved in preparing media. The second part of the book gives specific information for the preparation of culture media for the growth of various pathogenic organisms. Although emphasis is given to media published in the German literature, formulae of American and foreign origin are mentioned. The presentation is adequate and concise, the print is clear, and the book is arranged in alphabetical index form.

The Medical Clinics of North America: A Symposium from Philadelphia on Clinical Medicine. By numerous collaborators. Price, not given. Pp. 1,917, with 236 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

This number of "The Medical Clinics of North America" is entitled "A Symposium from Philadelphia on Clinical Medicine." Included are "Observations on the Management of Hypertension," by Charles C. Wolferth; "Some Clinical Expressions of Diffuse Collagen Disorders," by William S. Middleton; "Chemotherapy of Leukemia and Allied Disorders," by Byron E. Hall, and "The Management of Patients with Chronic Nonspecific Ulcerative Colitis," by T. Grier Miller. It is a well-rounded volume of general interest to those particularly interested in internal medicine.

Transactions of the Fourth Conference on the Adrenal Cortex, Nov. 12-14, 1952. Edited by Elaine P. Ralli, M.D. Price, $3.50. Pp. 165, with 31 illustrations. Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1953.

The four major topics taken up in this fourth Macy conference on the adrenal cortex include (1) the permissive action of adrenal cortex hormones, (2) mechanisms through which the adrenal cortex produces qualitatively different effects, (3) existence, nature, and site of production of a mineralocorticoid salt hormone secreted by the adrenal gland, and (4) adrenalectomy in man. With this as with so many of the other conferences one has ready at hand the great benefits of a brisk interchange of ideas by experts in this very complex and rapidly moving field. This has to be balanced against the tendency for dialectics and semantics at times to gain the upper hand so thoroughly that one is lost in the clouds of high echelon speculation. There can be no doubt that in this admirably edited conference report the fine points are in the ascendant. Although in general the construction of sentences and style is perfectly adequate, there are a few usages which trouble the occasional person whose sense of propriety is offended by an error which he hopes is confined to the participant's ability to use language rather than to use ideas or chemical tests. For instance, one finds the statement that epinephrine is a mechanism, that the ascorbic acid of adrenal glands from slaughter house beef is "50 to 75% in a beef gland." In several places the patients are operated, as though they were tractors rather than people being operated upon. In at least one place the comments make no sense unless one assumes that Cushing's syndrome has inadvertently been called Cushing's disease. Luetscher's name is spelled with pleasant informality, although this is undoubtedly one of

those words which is near the upper capacity of the human intellect to spell right anyhow. But these are trivial errors and no one, I think can write or edit a book without a few. The general information is not only extremely interesting and very stimulating but is current and timely. These conferences serve the very useful purpose of introducing the physician to an up-to-date view of the activity of one particular group of investigators who are the advanced picket guards of research. If the going at times passes through rarified atmosphere it is not because the participants have left the ground but rather that they are scaling the heights. In these days of adrenal ascendancy we can be grateful to be admitted into the transactions of such a company even though most of us will feel the awkward jealousy of the kibitzer.

Diseases of Muscle: A Study in Pathology. By Raymond D. Adams, M.D.; D. Denny-Brown, M.D., and Carl M. Pearson, M.D. Price, $16.00. Pp. 556, with 347 illustrations. Harper & Brothers, 49 E. 33rd St., New York 16, 1953.

This excellent monograph of diseases of muscle will become a vade mecum to workers in the field, and to those who, like the reviewer, have neglected to keep up to date on diseases of muscle, it will open up new fields of delight and fruitful contemplation.

The book is clearly written in an attractive, literary style, and the authors have made effective use of lead sentences in the paragraphs and of frequent summary sections. Often there is an introductory paragraph explaining the material to be covered in the chapter. These are models of clarity and condensation. The illustrations in the book are of uniformly high quality, well taken, and faithfully reproduced.

The book starts with a section on the normal anatomy, histology, embryology, and physiology of muscle. It then proceeds to a detailed consideration of the general principles of the reaction of skeletal muscle to injury, denervation, atrophy, and regeneration. Both of these sections are accompanied by an exhaustive bibliography.

The main portion of the book consists of a detailed consideration of the diseases of muscle, including pathological and clinical features. The congenital defects of skeletal muscle, muscular dystrophies, the inflammatory diseases, tumors, traumatic and circulatory diseases, spinal and neural muscular atrophies, and miscellaneous toxications due to toxic metabolic endocrine disturbances are all considered. The book ends with a brief consideration of differential diagnosis and methods of pathologic study.

The reviewer can not let this opportunity pass without offering congratulations to the authors and the publishers for giving us this fine monograph. It will long remain a cornerstone in the study of these obscure and interesting diseases.

Pituitary Chromophobe Adenomas. By John I. Nurnberger, M.D., and Saul R. Korey, M.D. Price, $7.00. Pp. 246, with 34 illustrations. Springer Publishing Co., Inc., 44 E. 23rd St., New York 10, 1953.

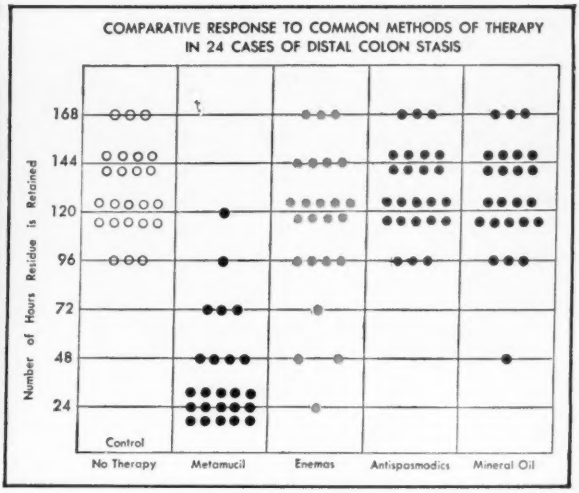
Pituitary adenomas of the chromophobe type have been described in great detail by the authors. Chapters on developmental anatomy of the pituitary gland, functional anatomy of the perisellar regions, and metabolic functions of the pituitary provide an excellent source of reference material.

Clinical chapters relate frequency of symptoms and signs as well as neurologic and metabolic accompaniments in 117 patients with pituitary neoplasia. Adequate discussion is given to laboratory procedures and pathologic findings in this condition. Therapy and therapeutic results are described.

Throughout the book the reader feels handicapped by awkward discussions of controversial points; by a formidable array of data, tables, and charts, and by a surfeit of references.

Despite these faults, the book is well supplied with useful facts and excellent illustrations. It provides valuable information for students of pituitary disease.

Distal Colon Stasis



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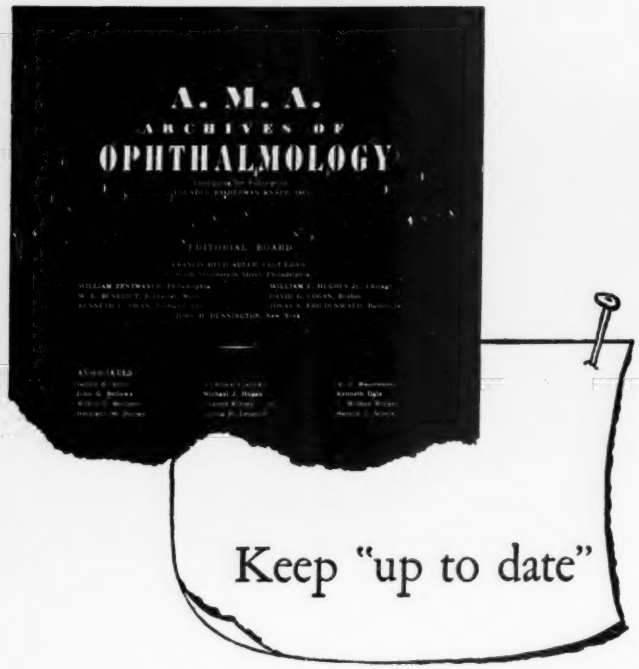

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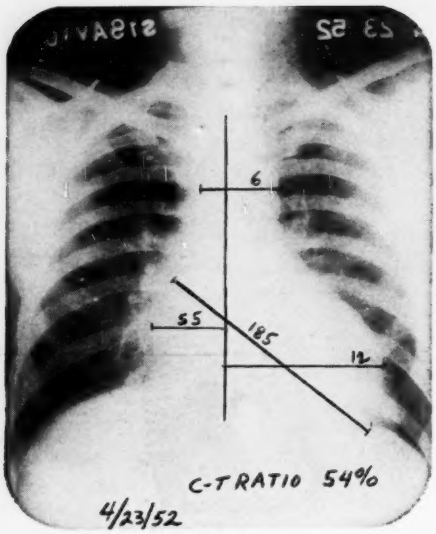
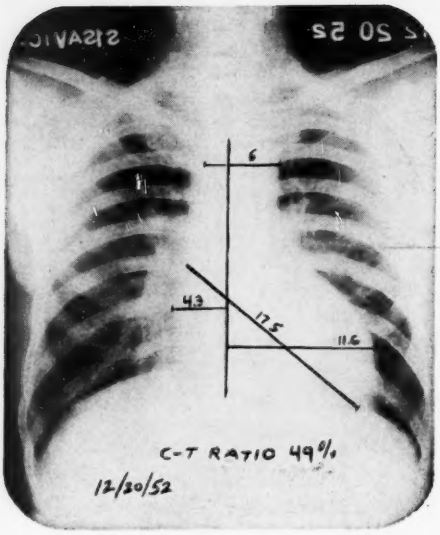


Patient F.S. before Methium: Cardio-thoracic ratio 54%, blood pressure 240/160 mm. Hg.[1]



After Methium: Cardio-thoracic ratio 49%, blood pressure 160/100 mm. Hg. This patient (F.S.) experienced no toxic side effects and did not lose a single day of work.[1]

Functional improvement from stabilized, lower blood pressure

In the first few months of therapy, over 80 per cent of the patients treated with oral hexamethonium have had gradual reduction in mean blood pressure of 20 mm. Hg or more.[2,3] With continued treatment, up to or beyond a year, this reduction can often be maintained with no serious side effects and *no increase in dosage.*[2]

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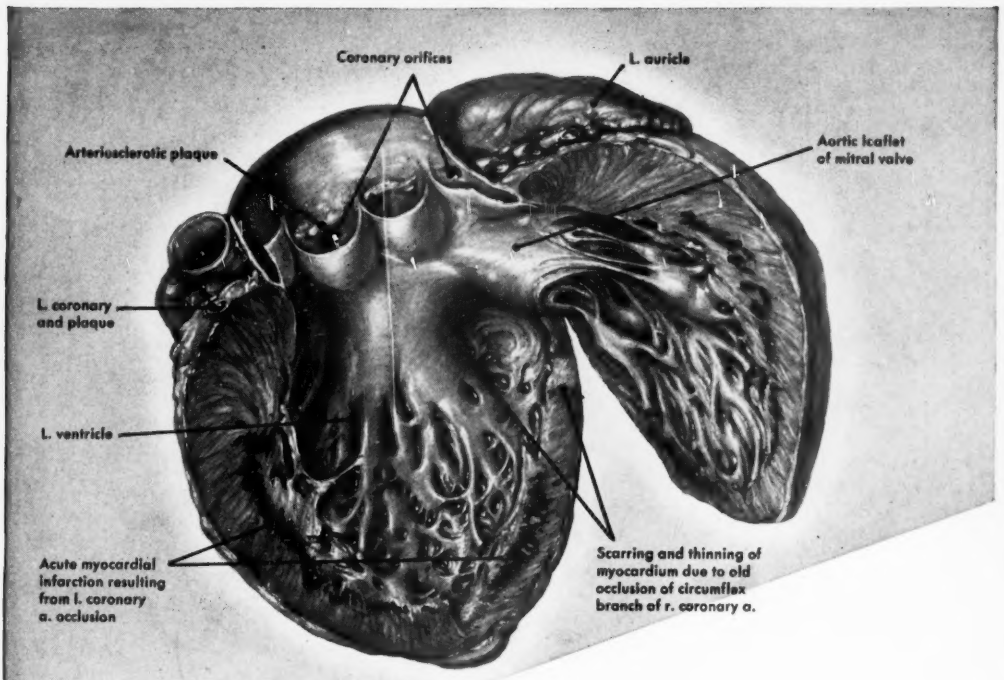
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"Severe cardiogenic shock demands therapy... the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

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therapy is generally well tolerated with initial low dosages, gradually increased.[1,2,3] Patient response is the guide to dosage adjustment.[4] Optimal maintenance dosage level is usually reached only after 3 weeks or more; marked therapeutic effect cannot be expected with initial low dosages.[4]

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